Prostate cancer: improving outcomes in Australia through rapid access diagnostics

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The University of Western Australia

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Declaration

This is to certify that this thesis does not incorporate, without acknowledgement, any material previously submitted for a degree or diploma from any university and that, to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Signed

Name

Date
Abstract

Prostate cancer is the most commonly diagnosed cancer in Australia with approximately 30,000 men diagnosed with the disease yearly. More men die of prostate cancer than women of breast cancer and, with earlier diagnosis, the potential of diagnosing localised prostate cancer – which is ultimately curable – is higher. The diagnosis of prostate cancer not only relies on history, examination findings, biochemical tests and radiological imaging, it also involves an invasive and potentially painful procedure – transrectal ultrasound (TRUS)-guided needle biopsy of the prostate. The main aim of this thesis is to test if a more tolerable TRUS-guided prostate biopsy can be achieved with the use of an anti-inflammatory.

A secondary aim of the study is to consider the differences in diagnosis, treatment and outcomes of prostate cancer for men residing in rural areas of West Australian (WA) compared with men residing in the Perth metropolitan area. Another aim is to conduct a feasibility study into whether the newly introduced ‘one stop’ prostate clinic (OSPC) would provide rapid and efficient assessment for Australian men, particularly rural patients.
Acknowledgements

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I would also like to thank my partner, Jean, and my parents for all their support and encouragement to never give up throughout this Master of Surgery program.
Statement of candidate contribution

This thesis contains published work and work prepared for publication, some of which have been co-authored. The bibliographical details of the work and where it appears in the thesis are outlined below.

Chapter 2


Wei Ling Ooi, Prof Dickon Hayne and Ronnie Cohen were involved in the conception and design of the study. WLO, Alex Brown and Sanjay Ramakrishnan were responsible for collating and analysing data. Drafting of the manuscript was performed by WLO, AB, RC and Prof DH. Abstract presentation at the USANZ ASM 2012 was performed by WLO.

Chapter 3


Wei Ling Ooi and Prof Dickon Hayne were involved in the conception and design of the study. WLO and Cynthia Hawks were responsible for collating and analysing data.
Drafting of the manuscript was performed by WLO, CH, Melvyn Kuan and Prof DH. Abstract presentation at the USANZ ASM 2012 was performed by WLO.

**Chapter 4**


Wei Ling Ooi was involved in the conception, design and execution of experimental work. WLO and Cynthia Hawks were responsible for patient recruitment and data collection. WLO performed data analysis with the help of an independent biostatistician. Drafting of the manuscript was performed by Wei Ling Ooi, Andrew Tan and Prof Dickon Hayne.
Publications and presentations from this thesis

Publications and presentations from this thesis were:


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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>ABS</td>
<td>American Brachytherapy Society</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Radiology</td>
</tr>
<tr>
<td>ADC</td>
<td>Apparent diffusion coefficient</td>
</tr>
<tr>
<td>ADT</td>
<td>Androgen deprivation therapy</td>
</tr>
<tr>
<td>AFS</td>
<td>Anterior fibromuscular stroma</td>
</tr>
<tr>
<td>AP</td>
<td>Anteroposterior</td>
</tr>
<tr>
<td>AS</td>
<td>Androgen suppression</td>
</tr>
<tr>
<td>AUA</td>
<td>American Urological Association</td>
</tr>
<tr>
<td>ASAP</td>
<td>Atypical small acinar proliferation</td>
</tr>
<tr>
<td>BCR</td>
<td>Biochemical recurrence</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CZ</td>
<td>Central zone</td>
</tr>
<tr>
<td>DCE</td>
<td>Dynamic contrast enhanced</td>
</tr>
<tr>
<td>DES</td>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td>DHT</td>
<td>Dihydrotestosterone</td>
</tr>
<tr>
<td>DRE</td>
<td>Digital rectal examination</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion-weighted imaging</td>
</tr>
<tr>
<td>EAU</td>
<td>European Association of Urology</td>
</tr>
<tr>
<td>EBRT</td>
<td>External beam radiotherapy</td>
</tr>
<tr>
<td>ESUR</td>
<td>European Society of Urogenital Radiology</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle-stimulating hormone</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>HDR</td>
<td>High dose rate</td>
</tr>
<tr>
<td>HGPIN</td>
<td>High grade prostatic intraepithelial neoplasia</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
</tr>
<tr>
<td>LDR</td>
<td>Low dose rate</td>
</tr>
<tr>
<td>LGPIN</td>
<td>Low grade prostatic intraepithelial neoplasia</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinising hormone</td>
</tr>
<tr>
<td>LHRH</td>
<td>Luteinising hormone releasing hormone</td>
</tr>
<tr>
<td>LUTS</td>
<td>Lower urinary tract symptoms</td>
</tr>
<tr>
<td>MAB</td>
<td>Maximum androgen blockade</td>
</tr>
</tbody>
</table>
Chapter 1
1. Introduction and historical review of prostate cancer

1.1 Background

Prostate cancer is the most commonly diagnosed cancer in Australia with 21,808 new cases diagnosed in 2009 (1, 2). Age-standardised incidence of prostate cancer has increased over time. There were 79 new cases per 100,000 males in 1982; by 2009 this figure had more than doubled (1). Further increase is expected in the future for a number of reasons, including public awareness (meaning more men present for testing), changes to diagnostic practices, and an ageing population.

The age-standardised mortality rate for prostate cancer in Australia has decreased over time, from 34 deaths per 100,000 males in 1982 to 31 deaths per 100,000 in 2011(1). Survival within the last 8 years for prostate cancer has been high and continues to improve. There was a 5-year survival rate of 92% between 2006-2010 (1). This survival rate is higher compared to other leading cancers in men such as melanoma of the skin (89%) and lung cancer (13%). This decline in mortality is forecast to reach 26 deaths per 100,000 males in 2020.

More importantly, men living in remote or very remote areas of Australia were less likely (150 per 100,000) to be diagnosed with prostate cancer compared to metropolitan areas. The differences between these population groups could be due to a number of reasons including rates of presentation for testing, population risk profiles and population age structures (1).
As reported by Australian Institute of Health and Welfare in their latest report in 2013, health expenditure on prostate cancer in Australia increased by 23% in 2008-2009 compared to the 2005 estimated expenditure of $349 million (1). This increase in expenditure has occurred as a result of both a higher number of cases and increased cost of treatments such as MRI and Robotic Surgery. Other than management of the disease, the expenditure includes cost of patients’ diagnosis as well as cost of organising travel and accommodation for rural patients to see specialist urologists in metropolitan hospitals.

The majority of patients would die with prostate cancer instead of from the cancer itself. Therefore, screening and diagnosis of prostate cancer has always been a controversial issue (3-5). However, the diagnosis of prostate cancer early is important because localised disease is potentially curable. Further, the consequences of advanced prostate cancer or metastatic disease impacts on quality of life and survival. For example, patients may suffer bladder outlet obstruction, rendering them incapable of passing urine, or have renal failure.

When patients present to the general practitioner (GP) with urinary symptoms they are examined via a digital rectal examination and undergo a prostate-specific antigen (PSA) blood test as part of general health screening for men. Depending on the results, this may lead to referral to a urologist for further investigation such as performing a trans-rectal ultrasound guided prostate biopsy (TRUS biopsy).
TRUS biopsy is commonly performed under local anaesthesia or sedation. Whilst having several advantages, local anaesthesia TRUS biopsy may still cause discomfort for some men. Thus, methods to improve tolerability of the procedure are desirable.

The main aim of this thesis is to examine if the diagnosis of prostate cancer involving TRUS-guided needle prostate biopsy can be made less painful.

A secondary aim of the study is to consider any differences in diagnosis, treatment and outcomes of prostate cancer for men residing in rural areas of West Australian (WA) compared with men residing in the Perth metropolitan area.

Another aim is to conduct a feasibility study into whether the newly introduced ‘One Stop’ Prostate clinic (OSPC) would provide an improvement in the diagnosis and management of this disease. This concept has been in use for many years in other parts of the world, such as the United Kingdom (UK), with the aim of facilitating rapid assessment of diseases. However, the ‘one stop’ approach is novel to Australia. In light of the fact that Australia is a country which has some of the most remote capital cities and towns in the world, a one stop approach is certainly worth considering.

The National Health Service (NHS) in the UK introduced the concept of the NHS Cancer Plan in 2000 to reduce wait times for diagnosis before treatment (6). The relationship between shorter wait times and increased survival for breast cancer formed the basis of reducing wait times to diagnosis of prostate cancer (7). The authors found a delay in 3-6 months of diagnosis were associated with lower survival. A 2-week wait ‘fast track’ system had been employed but was found to be non-sustainable. Patients suspected of having cancer had to be referred within 24 hours and seen by a specialist within 2 weeks.
In 2005, a new implementation of 31 days and 62 days was set out – the NHS wanted patients to be either treated within 31 days of decision to treat or within 62 days for treatment to occur from time of referral by the GP (8). With respect to urological malignancies, it was found that bladder cancer could be treated within these target timeframes but not achievable for prostate. Unlike bladder cancer, prostate cancer is a malignancy that requires more complex methods of diagnosis and decision-making regarding treatment pathways and thus treatment cannot comply with these target timeframes.

1.2 Prostate cancer

1.2.1 Aetiology

The prostate is a walnut shaped and sized organ that sits in the male pelvis at the base of the bladder. Its main function is to produce 20% of seminal fluid. It also produces PSA. Numerous genetic abnormalities are associated with prostate cancer, for example, inactivation of tumour suppressor genes PTEN (chromosome 10q) and p53 (chromosome 17p) (9, 10). Proto-oncogenes such as c-myc and blc-2 and prostate cancer susceptibility genes such as ELAC2/HPC2, CHEK2 and BRCA2 are also thought to be responsible for increased risk of prostate cancer (11-16).

Progression of prostate cancer is influenced by the male hormone testosterone and its metabolite, dihydrotestosterone (DHT). If these androgens are removed from a patient, apoptosis and involution of the prostate gland occurs. Castrated patients – including chemically castrated patients and those with congenital deficiency of 5 α-reductase which helps convert testosterone to its active metabolite DHT – do not get prostate cancer (17).
Food products such as soya which contains phytoestrogen, commonly used in Oriental cuisine, also have similar negative growth effect on prostate cancer. This may explain why there is a lower incidence and death rate from prostate cancer in parts of Asia where this produce is used widely (18). Vitamin E and selenium were also thought to be dietary substances preventative for prostate cancer. However, a large American trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) failed to prove that neither selenium nor vitamin E, alone or together, reduced the risk of prostate cancer (19).

There are two known histological lesions found on prostate biopsies which are regarded as pre-malignant lesions – prostatic intraepithelial neoplasia (PIN) and atypical small acinar proliferation (ASAP).

PIN demonstrates atypical cells histologically within the epithelium of the prostate gland. It is classified into low or high grade PIN (LGPIN / HGPIN). As there is no prognostic value in LGPIN, only the HGPIN is being reported. HGPIN is found in approximately 5-10% of prostate biopsies, with up to 45% risk of prostate cancer found on subsequent biopsies (20). The current recommendation is for repeat systematic biopsy at 12 months if multi-focal HGPIN is reported on initial biopsy or found on transurethral resection of the prostate (TURP). Repeat biopsy is recommended at 3 years if isolated HGPIN is found without other clinical indicators of cancer unless PSA kinetics prompt an earlier re-biopsy (17).

ASAP is a focus of atypical glands histologically suspicious for cancer. ASAP and HGPIN are different histologically. In up to 60% of cases, prostate cancer is diagnosed
following initial biopsy demonstrating ASAP (17). Repeat biopsy is warranted if ASAP is found as it is highly predictive of prostate cancer.

1.2.2 Risk factors

The cause of prostate cancer is not fully understood. However, research has found several risk factors associated with the development of prostate cancer – age, family history, ethnicity, and lifestyle and environmental factors.

The risk of developing prostate cancer increases with age. Less than 10% of cases are diagnosed in men less than 54 years of age, while 64% of cases are diagnosed between 55 and 74 years of age. Approximately one in five men are diagnosed with prostate cancer by the age of 85 (17).

Men with a first degree relative (parent, sibling or child) with prostate cancer are 2.2-2.8 times more likely to develop prostate cancer compared with other males (21). For men with two first degree relatives with prostate cancer, this risk increases to 3.5 times. Hereditary prostate cancer, such as those involving genetic abnormalities on chromosomes 1q, 8p, Xp and mutations of BRCA2 genes tends to occur in younger men (17).

Men of African descent are at greater risk of developing prostate cancer compared to Caucasian men. Asian or Oriental men are at low risk of prostate cancer unless they migrated to a Western country (17, 22). In Australia, there may be variation in prostate cancer diagnoses between ethnic groups as groups participate in screening at different rates or may have different access to healthcare services (23, 24).
Sexually transmitted infections, diets high in calcium and processed meats, and vasectomy were thought to be factors which could increase risk of prostate cancer. However, research looking into these factors has so far been inconclusive (25-27).

1.2.3 Diagnosis

Prostate cancer is often asymptomatic. It can be detected using PSA blood test and/or digital rectal examination (DRE). The screening of men aged 50-70 years old is acceptable and reduces significant mortality and morbidity caused by prostate cancer. These inexpensive tests can detect clinically significant disease before it leaves the prostate (17). In 2012, about 778,500 PSA test were performed in Australia; 80% were for men aged 45-74 (1).

The screening of men with life expectancy of less than 10 years, either due to age or co-morbidities, should be discouraged (28). The American Urological Association (AUA) guidelines recommends that men 70 years or above wishing to be screened for early detection of prostate cancer should have a life expectancy of greater than 10 years (29). Further, more men undergoing PSA screening should be counselled beforehand as there is evidence that PSA screening cause harms including complications of biopsy and side effects of treatment that may be unnecessary (30).

PSA is a glycoprotein produced by the prostate gland and disruption of the prostatic architecture by disease allows more PSA to leak into the bloodstream (17). PSA generally increases with increasing age but a PSA level which is higher than normal for a man’s specific age does not just indicate prostate cancer. With regards to prostate cancer, the
main uses for PSA test are (1) – to estimate the risk of prostate cancer, to prognosticate after diagnosis and to monitor success of treatment / detect recurrence.

The specificity of PSA test is dependent on the arbitrarily determined normal reference range. Specificity of the commonly used Osterling age-related reference ranges is low (40%) (17). Abnormally high PSA levels are not specific to prostate cancer; elevated levels could indicate benign prostate hyperplasia, infection or recent instrumentation. Therefore, it is not recommended that a single elevated PSA level should prompt prostate biopsy. The decision to undertake prostate biopsy should combine both PSA test and DRE. However, DREs can also sometimes be unreliable and are dependent on the experience of the examining doctor. It is often impossible to palpate the prostate gland in its entirety and some lumps in the prostate can be missed (31). Other factors such as free and total PSA, patient’s age, PSA velocity, PSA density, family history, ethnicity, previous biopsy history and co-morbidities should therefore be considered prior to recommending a patient undertake prostate biopsy (17) (Figure 1.1).
1.2.4 Grading

Prostate adenocarcinoma is graded using the Gleason system. The grading system uses a score system of 1-5 based on gland-forming differentiation histologically at low magnification. Both the primary (predominant) and the secondary (second most prevalent) histological patterns are identified and assigned a grade 1-5; 1 is most differentiated and 5 is least differentiated (2). The Gleason sum is obtained by adding the primary and secondary score. The system applies to all prostate biopsies, TURP and radical prostatectomy specimens. Occasionally, a tertiary Gleason score is reported on radical prostatectomy specimens – it represents the third most prevalent grade present on
the specimen. In 2005, the International Society of Urologic Pathology recommended that if the patient has a Gleason score of 3+4 or 4+3 prostate cancer with a tertiary score of Gleason 5, their Gleason score should be 8 or 9 respectively (32). This has prognostic significance if it is high grade (17) (Table 1.1).

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 to 4</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>5 to 7</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>8 to 10</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>

The Gleason score is a good prognostic indicator for prostate cancer. A patient who for example, has a Gleason score of 3+3=6 has better prognosis than someone with a Gleason score of 4+4=8. Patients of a similar Gleason score but with the predominant grade (the first score) which is higher would have worse prognosis. For example, a Gleason grade of 4+3=7 carries a worse prognosis than grade 3+4=7.

The D’Amico classification system was developed in 1998 as a predictive tool for prostate cancer progression (33). The system stratifies patients into low-, intermediate- or high-risk of biochemical recurrence (BCR) after radical prostatectomy or radiotherapy. It was based on clinical tumour, nodes, metastasis (TNM) stage, pre-operative or pre-treatment PSA level, and biopsy Gleason score. Low-risk patients were those with clinical T1c-T2a, PSA of 10ng/ml or less, and biopsy Gleason score of 6 or less. Intermediate risk patients were those with clinical stage T2b disease, PSA level of 10.1-20ng/ml, and biopsy Gleason score 7. High-risk patients were those with clinical stage T2c, PSA level greater than 20ng/ml, and biopsy Gleason score 8-10.
It should be noted that the grading using a Gleason score can also be affected by hormonal, radiation therapy or patients on 5α-reductase inhibitors (17). Reporting pathologists should be informed if patients are on the above therapy as this can affect the Gleason grading given.

1.2.5 Staging

Prostate cancer, like all cancers, is staged based on the TNM classification. The 7th edition Union Internationale Contre le Cancer (UICC) 2009 TNM is commonly used for staging (34) (Figure 1.2)
### Figure 1.2 UICC staging

<table>
<thead>
<tr>
<th>T</th>
<th><strong>Primary tumour</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically non-apparent tumour – not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour identified by needle biopsy (e.g. because of elevated PSA level)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within prostate gland</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves of one half of one lobe or less</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour involves more than half of one lobe but not both lobes</td>
</tr>
<tr>
<td>T2c</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends through the prostatic capsule</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator ani and / or pelvic wall</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th><strong>Regional lymph nodes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th><strong>Distant metastasis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Non-regional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s)</td>
</tr>
</tbody>
</table>

### 1.3 TRUS-guided prostate biopsy

#### 1.3.1 Anatomy of the prostate gland

The prostate gland has three glandular zones – the PZ, the central zone (CZ) and the TZ – and a fourth non-glandular zone, known as the fibromuscular stroma. These zones are fused together within a common sheath of fibromuscular tissue, the capsule. In a sagittal view, the prostatic urethra is divided into proximal and distal portions in equal length, divided by an anterior angulation at the midpoint between the prostate apex (distal) and
bladder neck (proximal) (35). The verumontanum protrudes from the posterior urethral wall at the angulation point. This is also the point where the ejaculatory ducts empty into the prostatic urethra. The ejaculatory ducts then extend towards the base (proximally) following a course that is a direct extension of the long axis of the distal (apex to mid-gland) urethral segment.

The PZ constitutes about 65% of a normal prostate gland and its ducts exit posterolaterally from the urethral wall on both sides of the prostate from the verumontanum to the prostate apex, with branches that curve anteriorly and posteriorly. The CZ makes up 30% of the glandular prostate gland and looks like a flattened conical structure. It has ducts arising on the verumontanum which branches out towards the base to surround the ejaculatory duct orifices. The TZ is the remaining 5% of the glandular prostate. It is best defined by the oblique coronal sections along the proximal (mid-gland to base) segment of the prostatic urethra from the verumontanum to the bladder neck. This zone is formed by two small lobes whose ducts leave the posterolateral recesses of the urethral wall. The TZ constitutes the bilateral regions in the middle to the base of the gland (along the proximal urethra) with ducts that extend laterally from the urethral wall and curves anteromedially.

The prostate gland is routinely described by its pathologic zonal architecture. These zones are divided into the anterior fibromuscular stroma (AFS), the TZ, the CZ, the periurethral zone and the PZ. These regions are not as distinct when viewed sonographically. However, the TZ may be distinguished from the PZ and the CZ in bigger prostate glands such as those in significant benign prostatic hyperplasia. Posteriorly, the normal CZ and the PZ from which the majority of prostate cancer arises have a homogenous echogenic
appearance (2) whilst the anteriorly situated TZ is more heterogeneous. The plane between the PZ and the TZ can also be discerned from each other using the calcifications along the surgical capsule known as corpora amylacea (36). Incidental findings of diffuse small calcifications are normal and represent age instead of pathology. Large prostatic calcifications are possibly associated to underlying inflammation and require further evaluation and treatment (37).

The prostatic urethra traverses the length of the prostate gland and its entire course can be imaged via the sagittal plane. Periurethral calcifications produce a thin echogenic outline sonographically. The smooth muscle of the internal sphincter can be visualised on the USS as a hypoechoic ring around the upper prostatic urethra, giving it a funnelled appearance proximally as it arises from bladder neck (2). The seminal vesicles are posterior to the prostate gland. In the transverse plane, the vas deferens travel above their ipsilateral seminal vesicles before diving caudally toward the prostate near the midline. The vasa and the seminal vesicles together form the ejaculatory ducts which are occasionally seen as a hypoechoic structure entering the gland posteriorly and empty into the urethra at the verumontanum.

1.3.2 History

In 1930, Ferguson performed the first needle biopsy of the prostate using a transperineal approach using an 18 gauge needle to aspirate the prostatic tissue (38). Astraldi then performed the first transrectal prostate biopsy in 1937 (39). In the 1980s, a transperineal ultrasound was fitted with biopsy apparatus to allow prostatic biopsy (40). This was then followed by a spring-loaded core biopsy device developed for use with a TRUS. It was
in 1987 that the first article was published describing the use of TRUS for transrectal prostate biopsy (40). The introduction of the systematic sextant biopsy protocol by Hodge et al. (41) further consolidated the usefulness of TRUS-guided prostate biopsy for the diagnosis of prostate cancer (42).

1.3.3 Indications

TRUS was initially used to detect rectal pathology. Takahashi and Ouchi first described the use of TRUS to assess the prostate in 1963 (43). The quality of the USS was suboptimal and its application in obtaining medically useful images was limited. In 1967, Watanabe first described clinically useful images of the prostate using TRUS (44). A 3.5 MHz ultrasound probe was used to obtain images and was at the time, considered state of the art technology (40). By the mid-1980s, the 7MHz ultrasound probe – which produced clearer definition of the prostate gland – became widely used by urologists.

Following abnormal DRE or PSA tests and further necessary counselling, the patient would be offered prostate biopsy. The following are indications for patients to undergo TRUS prostate biopsy (17):

- An abnormal DRE and / or elevated PSA.
- Previous biopsies which demonstrated pre-malignant prostate lesions such as multi-focal HGPIN or ASAP.
- Previous normal biopsies but rising PSA or abnormal DRE.
- To confirm recurrent prostate cancer following treatment (e.g. radiotherapy) if further treatment is being considered (e.g. salvage surgery).
Prostate cancer can also be diagnosed from surgery such as TURP where tissue diagnosis can be made from prostate chips sent for histopathology. In certain groups of patients – such as very elderly and frail patients with a clinically malignant prostate on digital rectal examination and a PSA >100ng/ml – it would be deemed unnecessary to perform an invasive procedure such as a TRUS prostate biopsy(17).

1.3.4 Biopsy

TRUS-guided prostate biopsy can be performed either under local anaesthetic, sedation or general anaesthetic. The TRUS provides the image of the prostate gland and seminal vesicles using a 7.5mHz biplane intrarectal probe measuring about 1.5cm in diameter (17) (Figure 1.3). Patients are place in the left lateral decubitus position with knees and hips flexed at 90 degrees. Usually, a careful DRE would precede TRUS prostate biopsy. Broad spectrum antibiotic (quinolones) is given before and after the biopsy. If the TRUS prostate biopsy is performed via local anaesthetic, approximately 10mls of lignocaine 1% is injected along the neurovascular bundles (NVBs) of the prostate. A 20 gauge spinal needle is used for this injection under TRUS guidance, starting from the seminal vesicles and moving outward to the apex. Measurements of the volume of the prostate gland would be obtained prior to performing the biopsy.
Abnormalities visible on TRUS prostate include hypoechoic or hyperechoic lesions in the peripheral zone (PZ) which could be due to either prostate cancer or inflammation. Most prostate cancers are isoechoic and not visualised on ultrasound scan (USS) (17). An 18 French Tru-Cut needle biopsy would typically include 10-12 biopsy specimens taken systematically. Some centres would include 14 core biopsies whereby biopsies would be taken from both sides of the prostate and include base, mid-gland, apex and transitional zones (TZs). If any hypoechoic or hyperechoic lesions are visualised on the TRUS prostate, these areas would also be biopsied.

The most common complications that could arise from having a TRUS prostate biopsy include (17):

- Vasovagal reaction immediately after biopsy.
- Urinary traction infection and, rarely, urosepsis which could be life threatening.
- Significant rectal bleeding – patients who are on anti-coagulants are advised to cease their anti-coagulants prior to the biopsy.

- Mild haematuria or haemospermia for up to several weeks post-procedure.

1.3.5 Techniques, probes and pathologies

TRUS of the prostate is the most common imaging modality used for the prostate gland. Its use is not confined to prostate cancer detection; it is also used in conditions such as infertility. The role of TRUS is primarily to guide biopsy of the prostate gland, its role in staging localised prostate cancer is limited.

Modern day TRUS probes are available in both side and end fire models which transmit frequencies of 6-10 MHz. The most commonly used is a 7MHz hand-held, high resolution probe with multi-axial planar image capabilities. It allows visualisation of transverse and sagittal views in real-time. Increasing the frequency also increases the resolution. A 7MHz transducer would produce a high resolution image with a focal range (the portion of the image that is in focus) from 1-4cm from the transducer which is ideal for visualisation of the PZ where most cancers arise (2). The older lower frequency transducers – 4MHz – have a longer focal range, from 2-8 MHz, but a lower resolution. The advantage of using lower frequency transducers is that it improves anterior demarcation of large prostate glands which gives better accuracy of volume measurements but poor internal architecture visualisation.

As ultrasound energy cannot propagate through air, a water-based medium which acts as a coupling medium such as ultrasound jelly or lubricant is used between the probe and rectum. Patients are placed in the left lateral decubitus position.
TRUS assessment of the prostate includes:

- Scanning the gland in transverse and sagittal planes to calculate volume
- Inspecting the CZ and PZ for hypoechoic lesions and abnormalities
- Visualising seminal vesicles and vasa deferentia

The TRUS machine has image magnification adjustment to allow the operator to adjust the visibility for visualisation of the entire gland and more focal lesions. For global view of the gland, the magnification is adjusted to low and, for biopsy, magnification is increased to allow visualisation of needle passage. The gain or brightness of the image can also be adjusted. The optimal brightness setting results in a medium-grey image of the normal PZ. This grey tone serves as the reference point for judging lesions as hypoechoic (darker than normal PZ), isoechoic (similar to normal PZ), hyperechoic (lighter than normal PZ) or anechoic (completely black) (2).

For transverse imaging, several techniques of probe manipulation can be used. Using radial or biplane probes, the probe can be advanced cephalad into the rectum to visualise the prostate base, seminal vesicles and bladder neck. If the probe is pulled caudally towards the anal sphincter, the prostatic apex and proximal urethra are visualised. Another method of producing transverse imaging is to angle the handle of the probe right or left using the anal sphincter as a pivot. The probe, when angled towards the scrotum, produces more cephalad images, whilst angling the probe toward the sacrum produces caudal images (2).
In order to yield sagittal images, there are two techniques. The first method is rotation of the probe. If the probe is rotated clockwise, the left side of the prostate is visualised; counter clockwise rotation produces images of the right side. Similarly to transverse imaging, sagittal imaging can also be produced by angling the probe up or down using the anal sphincter as a pivot. When the handle of the probe is angled down (toward the floor) for a patient in lateral decubitus position, the right side of the prostate is imaged and turning the probe up (towards the ceiling) produces images on the opposite side.

Dual transducer probes used for TRUS prostate biopsy allow a dual function – simultaneous biplane imaging and endfire imaging. The probes are designed on an ‘iso-centre’ principle whereby the scanning planes intersect with each other. The sagittal array of the probe forms a 210° arc. A section of the sagittal array and transverse array provide simultaneous biplane scanning which allows both sagittal and transverse views to be displayed on the screen monitor. These probes can also be changed to endfire imaging whereby the display can allow for more accurate targeting of the lesion for biopsy after being viewed in both sagittal and transverse views.

Volume calculations of the prostate gland involve measurement of three prostate dimensions – transverse, anteroposterior (AP) dimensions and longitudinal dimension – measured in the sagittal plane. The AP dimensions are measured at the point of widest transverse diameter. On measurement of these dimensions, the TRUS machine calculates the volume of the prostate, with 1cm³ approximately equating to 1g of prostate tissue. Average prostate size is 20-25g with the size increasing beyond the age of 50.
If a more accurate measurement of volume is required such as in brachytherapy, planimetry may be employed (2). The patient is placed in lithotomy position, the probe is mounted to a stepping device and serial transverse images are obtained through the entire length of the gland. The surface area of each serial image is ascertained and the sum of these measurements is multiplied by total gland length to obtain the prostate volume. PSA density (serum PSA/gland volume) can be calculated once a gland volume has been obtained. It is useful for predicting prostate cancer diagnosis and has also been found to be a significant predictor of different indices of aggressive cancer (45).

The majority of cancers (70%) originate from PZ, 10% from the CZ and 20% from the TZ (46). Prostate cancer typically appears as a hypoechoic lesion in the PZ. Other diseases such as granulomatous prostatitis, prostatic infarct and lymphoma can appear hypoechoic (47-49). There are cancers which can have isoechoic or hyperechoic appearances on TRUS. Even if there is no hypoechoic lesion present in the PZ on TRUS, current practice recommends that systematic 10-12 core biopsies be performed (50).

Recently, three-dimensional (3D) TRUS probes have been introduced for the imaging and therapy of prostate cancer including prostate biopsies, detecting brachytherapy seeds and evaluating prostate volume. Chen et al. (51) proposed that a 3D TRUS probes improved image acquisition, particularly for prostate tumour volumes with high variable geometry. The authors also highlighted that although a two-dimensional (2D) TRUS can provide similar information as a 3D TRUS, it is still highly operator-dependent and therefore the accuracy of the actual volume measurement and biopsy can be affected.
A 3D TRUS can also be combined with magnetic resonance imaging (MRI) or computed tomography (CT) to provide better imaging and ultimately diagnostic or therapeutic procedures. Ukimura et al. (52) found that prostate biopsy accuracy was improved when 3D TRUS prostate biopsy was combined with MRI. The authors used a 3D TRUS probe (3D5-9EK) and an Accuvix-V10 ultrasound machine [Samsung Medison America] capable of acquiring 3D images. The system uses a computer system called Urostation which has two functions – firstly, to create a real-time TRUS image guided by a computer-assisted, real-time 3D TRUS registration system to spatially map each biopsy needle trajectory using elastic image fusion of each 3D prostate model; and secondly to create a magnetic resonance (MR)/TRUS fusion guidance using elastic between the 3D prostate model of pre-operatively acquired MR and that of real-time 3D TRUS.

Ukimura et al. found that by using this 3D MR/TRUS fusion technology for prostate biopsy they were able to accurately identify and biopsy prostate lesions which were both hypoechoic and isoechoic. From the 27 prostate biopsies performed in their study, 100% hypoechoic lesions and 89% isoechoic lesions were successfully targeted. The mean total targeting error of needle for both types of lesions was less than 3mm. One of the main advantages of this technology is its ability to record needle track pathways – if a lesion requires re-biopsy this can be done accurately. This cannot be achieved in conventional TRUS prostate biopsy. This is particularly relevant to patients undergoing active surveillance or those that require further intervention such as brachytherapy.

When TRUS prostate biopsy was first performed, a sextant, or six, core biopsy was performed; one sample was taken from the apex, base and mid-prostate on each side (53).
However, approximately 15% of prostate cancer was found to be missed from sextant biopsies (54). Patients were also requiring repeat biopsies as initial sextant biopsies missed prostate cancer in their initial biopsies (55). Other limitations included the unreliability of sextant biopsies in monitoring the tumour status in patients who elected to have watchful waiting or less invasive therapy (56). Therefore, the sextant biopsy was eventually replaced by extended core biopsy.

Extended TRUS prostate biopsy involves obtaining five to seven core biopsies on each side of the prostate, with sampling more focused on the lateral aspects (55, 57, 58). A systematic review of extended core biopsy by Eichler et al. (59) concluded that 12 core schemes with laterally detected cores detected 31% more cancers. Adverse events for 12 core biopsies were similar to sextant biopsies (Figure 1.4)
Figure 1.4  Extended 14 core prostate biopsy

X denotes biopsy site

An alternative method of obtaining prostate biopsy is via the transperineal method. It has the advantages of reduced sepsis as rectum not traversed and better sampling of the anterior zone. Its disadvantages include increased cost as GA is required and increased risk of acute urinary retention. In rare circumstances, this method is useful for patients who have had previous abdomino-perineal resection or severe anal stenosis. Some centres in Asian and Europe prefer this method of prostate biopsy (60). Studies from Japan demonstrated that extended transperineal (12 core) prostate biopsy had similar detection rates of cancer compared to transrectal prostate biopsy (60, 61). One centre in Australia found that transperineal prostate biopsy detected more anterior tumours (16.2% vs 12%)
and identified them at a smaller size and stage compared to transrectal biopsy (62). Similarly, transperineal biopsy has also been found to detect significant cancer in patients with repeated negative biopsies and elevated PSA in a study by a group in Norway (63). The authors found that the transperineal approach provided greater yield of detecting cancers particularly in the anterior region of the prostate.

Shen et al. (64) – in their review article comparing transperineal and transrectal approach for prostate biopsy – showed comparable results for complication results in both approaches. This is also supported by another study performed by Miller et al. (65) where the authors recommended the use of transperineal prostate biopsy instead of the transrectal approach for patients who would poorly tolerate infection from the procedure. Pepe et al. (66) found that the complication rates significantly correlated with the number of core biopsies performed. Patients who underwent 12 core transperineal biopsies had statistically significantly less complication rates in comparison to those who underwent greater than 24 core biopsies (31.5% versus 57.4%). Haematospermia was the most common complication in these patients, followed by haematuria.

Transperineal TRUS prostate biopsy is often performed with the assistance of radiological methods such as USS or MRI. Another method of transperineal biopsy of prostate is using a template guide brachytherapy template. This technique of biopsy is often used following repeated negative biopsies and before patients enter the pathway of active surveillance or focal therapy (67). The technique involves obtaining 5mm intervals core sample throughout the prostate with more number of cores taken, up to 50 cores (68). It provides detailed and more targeted sampling of the prostate. Onik et al. (68) found that
transperineal mapping prostate biopsy increased staging of patients’ prostate cancer –
22.7% of patients had Gleason scores increased to 7 or higher. The complication rates
were also acceptable considering the large number of cores taken and that none of the
complications resulted in death. However, the authors acknowledged that the downside
of performing prostate biopsy via this technique involves a higher cost, general
anaesthesia or sedation, and an increased number of cores (which also involves a heavier
cost for pathological processing).
Publication


Wei Ling Ooi, Prof Dickon Hayne and Ronnie Cohen were involved in the conception and design of the study. WLO, Alex Brown and Sanjay Ramakrishnan were responsible for collating and analysing data. Drafting of the manuscript was performed by WLO, AB, RC and Prof DH. Abstract presentation at the USANZ ASM 2012 was performed by WLO.
2. Prostate cancer in WA: urban–rural differences

2.1 Introduction

Prostate cancer services in Australia are generally located in major centres. As such, it has been postulated that the 15-30% of WA men living in rural locations may therefore be diagnosed later than their urban counterparts and subsequently have worse disease profiles (69). Published data have also shown that prostate cancer mortality is higher for rural patients compared to urban patients (70).

The urban–rural disparity is highly relevant in WA. A huge proportion of the state is covered by rural areas and patients living in these areas should have equal optimal healthcare. WA has an estimated land size of 2.5 million km² and makes up one third of the total land in Australia (71). Approximately 14% of the population in WA lives in rural or remote areas (72). Although rural patients receive financial assistance from the government for the cost of their travels to see a specialist via the patient-assisted travel scheme (PATS), there is still significant burden attached to time and cost for the patient.

As such, many previously published studies of WA patients have looked at the differences in quality of care in rural medicine and attitudes of rural patients towards their health (73, 74) but none had quantified the differences in urban–rural disease profile, particularly in prostate cancer. The aim of this study was to quantify the differences in the rate of prostate cancer diagnosis and disease profile in urban and rural men undergoing prostate needle biopsy in WA. From the data, we also examined demographic and radical prostatectomy
rate differences in these men to determine if an association exists between worse disease profiles and management offered.

2.2 Methods

The study included 7561 WA men recorded in the WA Prostate Biopsy Database between September 1998 and August 2006. The database represents more than 80% of all prostate cancer biopsy specimens in WA (based on Medicare data). All histopathology was performed by a single pathologist. Based on the Australian Bureau of Statistics remoteness area (RA) classification, these patients were segregated into urban (RA1 and RA2, 6525 men) or rural (RA3 to 5, 1036 men) locality based on their corresponding postcodes. Exclusion criteria were patients who had previously undergone prostate biopsy at any institution, regardless of outcome, and those with prostate cancer previously diagnosed on TURP. This research was approved by the Hollywood Private Hospital Research Ethics committee.

Initially, 7571 men who underwent initial prostate biopsy were found in the database. Ten patients had to be excluded from the analysis as their addresses were not listed or they were interstate or overseas patients. Demographic analysis included age, PSA level, TRUS volume, PSA range, number of cores taken for biopsy and initial biopsy outcomes. Additionally, Gleason sum, Gleason grade, tumour length and extent of prostate cancer were further analysed. Comparison was also made for the number of urban and rural patients who underwent radical prostatectomy.
All statistical analyses were performed using SPSS 17.0 for Windows. Rural and urban groups were compared using non-parametric methods – the Kruskall-Wallis test for continuous variables and the \( \chi^2 \) test for categorical variables. \( p \) values were two-sided with an accepted statistical significance level of \( p<0.05 \).

### 2.3 Results

Our initial analysis included 7561 WA men (6525 urban, 1036 rural) who had an initial TRUS prostate biopsy between September 1998 and August 2006. A summary of their demographic differences is presented in Table 2.1. Rural men were found to have a higher PSA compared to men of urban locality. Proportionally, more rural men had a PSA greater than 10ng/ml compared to their urban counterparts – 37.4% versus 31.9% (\( p=0.001 \)). Our data also revealed that a higher proportion of rural patients (62.6%) compared to metropolitan patients (58.4%) were diagnosed with prostate cancer (\( p=0.01 \)).

We found 4460 men (3811 urban, 649 rural) diagnosed with prostate cancer after their initial biopsy. We discovered several differences in terms of age, PSA level, number of biopsy cores, extent of prostate cancer, and advanced Gleason grade, and in the number of patients who went on to have radical prostatectomies. Men from rural localities were slightly younger – mean age of 65.7 years versus 66.9 years, \( p=0.005 \). Their median PSA levels were higher compared to their urban counterparts – 9.6ng/ml versus 8.6ng/ml, \( p<0.0001 \). The number of cores taken for rural patients were less – median = nine cores compared to 11 for urban patients, \( p<0.0001 \).
Table 2.1  Demographics of WA patients who underwent initial prostate biopsy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Urban patients</th>
<th>Rural patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Total number</td>
<td>6525</td>
<td></td>
<td>1036</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>65.1 (65.0)</td>
<td></td>
<td>64.5 (64.0)</td>
</tr>
<tr>
<td>Range</td>
<td>23-97</td>
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<td>38-91</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
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<td></td>
<td></td>
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<tr>
<td>Mean (median)</td>
<td>17.9 (7.6)</td>
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<td>35.6 (8.5)</td>
</tr>
<tr>
<td>Range</td>
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<tr>
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<td>4.1-10ng/mL</td>
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<td>1975</td>
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<td>365</td>
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<td>9.2 (9.0)</td>
</tr>
<tr>
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<tr>
<td>Cancer</td>
<td>3811</td>
<td>58.4</td>
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</table>

* PSA values missing for 395 patients

Proportionally, more rural patients had a higher Gleason grade sum of 8-10 compared to urban patients – 22.5% and 18.7% respectively (p=0.023). The extent of prostate cancer is defined as the number of cores positive out of the total number of cores taken. Our data revealed that rural patients had higher extent of prostate cancer – 45.5% versus 38.5% (p=0.002). Interestingly a smaller proportion of rural patients diagnosed with prostate cancer went on to have radical prostatectomy compared to urban patients – 27.1% and 31.2% respectively (p=0.037) (Table 2.2).
Table 2.2  Demographics and tumour characteristics of WA patients who underwent initial prostate biopsy with a diagnosis of prostate cancer

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Urban patients</th>
<th>Rural patients</th>
<th>p value</th>
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<td>Range</td>
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<td>PSA, ng/mL</td>
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<td>Mean (median)</td>
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<td>50.9 (9.6)</td>
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<td>Biopsy scheme (cores)</td>
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<tr>
<td>Mean (median)</td>
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<tr>
<td>Range</td>
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<tr>
<td>Gleason sum</td>
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<tr>
<td>≤ 6</td>
<td>1124</td>
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<tr>
<td>7 (3+4)</td>
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<td>7 (4+3)</td>
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<td>8-10</td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>1189</td>
<td>31.2</td>
<td>176</td>
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</tbody>
</table>

Table 2.3 demonstrates the comparison of demographics and tumour characteristics of 1175 WA men from our dataset who underwent radical prostatectomy. More rural patients
were found to have lower Gleason score (≤6) at time of radical prostatectomy compared to metropolitan patients – 26.8% versus 19.5% (p=0.032).

Table 2.3  Demographics and tumour characteristics of WA patients who underwent radical prostatectomy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Urban patients</th>
<th>Rural patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Total number</td>
<td>1189</td>
<td>176</td>
<td></td>
</tr>
<tr>
<td>No. in dataset</td>
<td>1011</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td><strong>Age at surgery years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>60.5 (61.0)</td>
<td>60.1 (60.0)</td>
<td>0.453</td>
</tr>
<tr>
<td>Range</td>
<td>40-79</td>
<td>44-73</td>
<td></td>
</tr>
<tr>
<td><strong>PSA, ng/mL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>7.7 (6.5)</td>
<td>8.1 (7.0)</td>
<td>0.150</td>
</tr>
<tr>
<td>Range</td>
<td>0.7-50.0</td>
<td>1-29.1</td>
<td></td>
</tr>
<tr>
<td><strong>Days between biopsy &amp; surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>76.1 (57.0)</td>
<td>69.4 (55.0)</td>
<td>0.079</td>
</tr>
<tr>
<td>Range</td>
<td>7-1476</td>
<td>8-839</td>
<td></td>
</tr>
<tr>
<td><strong>Prostate weight (grams)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>43.3 (40.0)</td>
<td>45.4 (42.5)</td>
<td>0.101</td>
</tr>
<tr>
<td>Range</td>
<td>9-194</td>
<td>20-119</td>
<td></td>
</tr>
<tr>
<td><strong>Gleason sum – index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>6.8 (7.0)</td>
<td>6.7 (7.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Range</td>
<td>5-9</td>
<td>5-9</td>
<td></td>
</tr>
<tr>
<td><strong>Index Gleason grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>197</td>
<td>19.5</td>
<td>44</td>
</tr>
<tr>
<td>7 (3+4)</td>
<td>504</td>
<td>50.0</td>
<td>75</td>
</tr>
<tr>
<td>7 (4+3)</td>
<td>252</td>
<td>25.0</td>
<td>38</td>
</tr>
<tr>
<td>8-10</td>
<td>56</td>
<td>5.6</td>
<td>7</td>
</tr>
<tr>
<td><strong>% Gleason grade 4/5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>35.2 (30.0)</td>
<td>32.2 (30.0)</td>
<td>0.247</td>
</tr>
<tr>
<td>Range</td>
<td>0-100</td>
<td>0-100</td>
<td></td>
</tr>
<tr>
<td><strong>Zone of index tumour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TZ</td>
<td>147</td>
<td>14.5</td>
<td>37</td>
</tr>
<tr>
<td>PZ (or CZ)</td>
<td>862</td>
<td>85.3</td>
<td>127</td>
</tr>
<tr>
<td><strong>Index tumour volume (cc)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>3.3 (2.6)</td>
<td>3.8 (2.5)</td>
<td>0.891</td>
</tr>
<tr>
<td>Range</td>
<td>0-44.9</td>
<td>0.1-37.9</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour locations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PZ / CZ</td>
<td>979</td>
<td>96.8</td>
<td>158</td>
</tr>
<tr>
<td>TZ</td>
<td>498</td>
<td>49.3</td>
<td>84</td>
</tr>
<tr>
<td><strong>Intraduct carcinoma</strong></td>
<td>189</td>
<td>18.7</td>
<td>29</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----</td>
<td>-----</td>
<td>----</td>
</tr>
<tr>
<td><strong>Insignificant cancer</strong></td>
<td>34</td>
<td>3.5</td>
<td>7</td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total performed</td>
<td>430</td>
<td>42.5</td>
<td>49</td>
</tr>
<tr>
<td>Proportion of total performed that are positive</td>
<td>2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Post-operative follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number with available follow-up</td>
<td>1004</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td><strong>Length of follow-up, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (median)</td>
<td>4.5 (4.7)</td>
<td>4.3 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.1-11.8</td>
<td>0.1-9.7</td>
<td></td>
</tr>
<tr>
<td><strong>0.2ng/mL BCR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>221 / 1004</td>
<td>22.0</td>
<td>34 / 161</td>
<td>21.1</td>
</tr>
<tr>
<td><strong>Post-operative treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated for BCR, rising PSA or adverse pathology</td>
<td>210</td>
<td>20.9</td>
<td>28</td>
</tr>
<tr>
<td>BCR but no treatment</td>
<td>65</td>
<td>6.5</td>
<td>11</td>
</tr>
<tr>
<td>No failure or treatment</td>
<td>729</td>
<td>72.6</td>
<td>122</td>
</tr>
</tbody>
</table>

* Gleason grade missing for two RA1&2 where no prostate adenocarcinoma was identified at radical prostatectomy

### 2.4 Discussion

There is increasing evidence that rural patients have worse outcomes from their disease compared to their metropolitan counterparts. Several studies – both in Australia and overseas and including several centres – have reported worse outcomes for rural patients (75-80). A study conducted in New South Wales showed that patients living in remote areas were three and a half times more likely to die from prostate cancer and cervical cancer than patients who lived in areas of highly accessible medical care (79). Our analyses have shown that rural patients in our particular population were diagnosed with worse prognosis disease than metropolitan patients and may have been offered curative
intent treatment less frequently. Coory et al. (75) also found that less rural patients underwent radical prostatectomy compared to metropolitan patients. Other authors also found that those of lower socio-economic groups were significantly less likely to undergo radical prostatectomy (80, 81). Better access to urologists in capital cities may explain higher rates of radical prostatectomy for patients residing in these areas (75). Financially advantaged men or those with private health insurance were also more likely to be offered radical prostatectomy for prostate cancer treatment (80, 82, 83).

Rural men in Australia are generally linked to lower educational level and lower socio-economic group (84). Some authors reported an association between lower education and higher likelihood of undergoing radiotherapy as opposed to surgical treatment for prostate cancer (82). Again, this could potentially explain lower rates of radical prostatectomy in our rural group. Interestingly, operated rural patients were found to have a lower Gleason sum at radical prostatectomy. This further suggests a selection bias in rural patients being offered surgery.

It is not understood why mortality rates for rural patients with a diagnosis of cancer are significantly higher compared to their urban counterparts (75). Some studies have examined the relationship between access to healthcare and mortality rates of the same population (76, 77, 85) and found that the rural population were disadvantaged. Delayed presentation to GPs for PSA testing for rural patients in our population may have been a factor delaying these patients’ diagnosis and therefore may end up with more advanced stage of prostate cancer at diagnosis. A study from the GPs’ perspective pointed out several factors that could influence delay in rural patients’ presentation to a GP,
particularly in WA. Seasonal work, co-morbidities that mask symptoms, informal social networks on health decision making and difficulty scheduling medical appointments were amongst the factors found to delay cancer diagnoses in the rural population (69, 74, 84).

Differences in health attitudes may explain why rural patients have poorer outcomes in cancer diagnosis. Rural patients are perceived as being less proactive in taking control of their health and often seek help at a stage when curative treatment is no longer possible. Studies on the health attitudes of rural Australian patients found that these patients adopted higher levels of stoicism and fatalism (84). Rural patients in WA have been found to have poor appreciation on actual survival rates for various cancers and this is one possible factor accounting for fatalistic attitudes (86). These attitudes were linked to patterns of advanced diagnoses and eventually poorer prognoses (74, 84). Our study did not specifically address differences in health attitudes between population– potential future studies may answer this particular question.

Differences in prostate cancer screening between urban and rural patients can account for inequality in disease outcomes. Baade et al. (87) have demonstrated discrepancy in rural prostate cancer screening. Rural patients in Australia had lower rates of PSA testing and radical prostatectomy with poorer survival and mortality outcomes. Other studies also found evidence suggesting that the urban–rural inequality for prostate cancer mortality could be associated with differing intensities of screening (85). Lower socio-economic status and education levels, both associated with rural population combined with limited knowledge of prostate cancer, are more likely to be associated with higher prostate cancer mortality (74, 78). A study which examined public health and disparities between
different populations in the United States also demonstrated that rural origin itself would result in less uptake of cancer screening (78). In addition, countries that do not adopt systematic screening programs were found to have more distinct urban–rural discrepancies in overall prostate cancer screening rates (85).

Several recommendations have been made to equalise rural and urban patients’ cancer outcomes. One author recommended regular visiting surgeons and multi-disciplinary teams to rural areas, increasing resources for rural surgeons, or bringing rural patients to metropolitan areas (80). In this specific context, we encourage cancer services to target a facility specifically for rural patients such as “One Stop” prostate clinics. These rapid access diagnostic services can spare rural patients multiple trips to a metropolitan centre and may reduce chances of patients being lost to follow-up. This will be discussed in the next chapter.

WA prostate needle biopsy patients from rural locations had a higher rate of cancer diagnosis and higher grade tumours than men from urban centres. This may be a result of suboptimal or delayed access to healthcare. In addition, a lower incidence of rural patients underwent radical prostatectomy, possibly reflecting a higher grade disease at diagnosis and selection bias.
Chapter 3

Publication

3. The one stop prostate clinic (OSPC): analysis

3.1 Introduction

As already discussed, prostate cancer is the most common cancer in Australian men and the second most common cause of cancer deaths in men. Each year in Australia, about 20,000 new cases of prostate cancer are diagnosed in Australia. Of these, approximately 3,300 men in Australia die from prostate cancer which surpasses the number of women who die from breast cancer (89). Rural and regional Australian men have a 21% higher mortality rate than that of their urban counterparts (1).

As such, the concept of a rapid assessment prostate clinic is desirable for a vast state such as WA. The state is sparsely populated and about one third of its population live in rural areas. A lack of services in rural Australia means country patients are disadvantaged as there is poorer access to services in tertiary centres where urologists are based. This can lead to diagnosis and management delays. Visiting urologists try to extend specialist services to these areas but these visits are usually limited in frequency and access to essential tools such as TRUS prostate biopsy facilities. This is inadequate for a population where there is a higher mortality rate from prostate cancer (87).

No national program where a rapid assessment prostate clinic is in place in Australia. Our centre has taken the initiative to implement a rapid access diagnostic service for rural men at risk of prostate cancer – the OSPC.

The rapid assessment prostate clinic, better known as the ’One Stop’ Prostate clinic was established in August 2011 primarily for rural patients. The clinic was promoted to rural
GPs via the Cancer Council WA network and the rural GP networks. It was a fortnightly clinic which took place at the endoscopy unit in Fremantle. Two nurses were assigned to the clinic – one to assist in the biopsy and the other to perform pre-procedural checklist and post-procedural observations. Abstracts written about this clinic were also presented at USANZ national and state (WA) meetings. Rural GPs referred patients based on a proforma (see Appendix 1) prepared by the urology consultant who headed the clinic.

3.2 Methods

3.2.1 Referrals to the OSPC

The patients who were referred to the clinic fit one of the following criteria:

- Hard, irregular prostate on DRE.
- Suspicious feeling prostate on DRE – even with normal PSA for age-specific reference range.
- Raised / rising PSA (age-specific) +/- LUTS.
- Prostate cancer-related symptoms and high PSA levels.

GPs were also advised to ensure patients did not have urinary tract infections when the PSA levels were tested to avoid false positive PSA elevations. Discussion between the GP and urologist could take place in special circumstances as to the appropriateness of referring patients to this clinic in instances when patients were known to have multiple co-morbidities or were elderly. GPs were also advised to cease anti-coagulants for patients attending the clinic in preparation for a potential TRUS prostate biopsy.
3.2.2 Attendance at the OSPC

Once a referral has been received and approved, the patient’s attendance was coordinated by the OSPC nurse. The patient received a letter confirming the clinic appointment with date and clinic times, and an information sheet regarding the clinic which included further information about TRUS-guided prostate biopsy (Appendix 3).

On the mornings of the clinic, the urologist performed a full urological assessment. If appropriate, the patient then underwent a local anaesthetic TRUS-guided prostate biopsy in the same visit. The normal practice was for the urologist to perform 14 core biopsies using a 18G Bard® core biopsy needle. Occasionally, less core biopsies were obtained if clinically indicated, for example, in patients with clinically obvious locally advanced disease. The biopsies were taken after periprostatic infiltration of 10mls 1% lignocaine local anaesthetic and all biopsy samples were examined by the same specialist urology pathology service (Uropath®). Patients were discharged home once they voided or there were no immediate complications following biopsy. Patients were also told that they would receive a telephone follow-up within a week from the OSPC nurse who would provide results of their biopsy and identify if there were any complications occurring from the biopsy. They were also informed if any further follow-up needed to be arranged.

3.2.3 Follow-up

The urologist reviewed pathology results to determine appropriate follow-up. All prostate biopsy results were also discussed at the centre’s multi-disciplinary meeting which ensured that patients had suitable management plans and were not lost to follow-up. Patients then received a phone call from the OSPC nurse informing them of the pathology results and any further follow-up plans. If prostate cancer was found on the biopsy, the
patient was informed of this but no specific detail of Gleason grade, disease volume or potential treatment was discussed. At the same time, any complications which occurred was recorded by the OSPC nurse and further follow-up appointments or staging investigation were also organised by the nurse. The patient’s GP also received a letter which informed them of the outcome of the clinic visit, result and future management plans. In addition, for patients newly diagnosed with prostate cancer, the OSPC nurse liaised with the rural cancer nurses with regards to providing support and information for these patients.

3.2.4 The difference between traditional referral and OSPC pathway

Traditionally, patients were referred by GPs and the referrals triaged based on clinical urgency. Patients then received a clinic appointment to have their history taken and clinical examination performed. If necessary, patients then were booked for TRUS-guided prostate biopsy. If they were country patients, further trips were necessary to return for prostate biopsy. Following biopsy, another clinic appointment was then made to follow-up on results and to discuss management. The OSPC took away the extra outpatients’ visits for the biopsy and, in some cases, unnecessary further clinic appointment if results were negative for prostate cancer (Figure 3.1).
Figure 3.1  Comparison of OSPC model to standard outpatient care model
Figure adapted from McCombie et al. (90). Adapted with permission from author.

3.2.5  Data collection

We collected data prospectively on the first 100 patients who attended the clinic between August 2011 and October 2012. Age, wait times from referral, diagnosis, follow-up treatments, choice of local or general anaesthetic for repeat biopsy and patients’ overall satisfaction level (good, satisfactory or poor) were recorded.
3.3 Results

3.3.1 Patient characteristics

The median age of the patients was 62 years, with a range of 38-85 years. During the data collection period, our median wait time from referral date to clinic date was 28 days (range 1-148 days). As a comparator, an audit of 20 men undergoing prostate biopsies via the standard pathway showed a median (range) referral to biopsy time of 188 (51-425 days). In the first 15 months of commencing the clinic, the first 100 patients were seen.

3.3.2 Histopathology

The majority of our patients were diagnosed with prostate cancer – 50% (n=50). The next most common diagnosis was HGPIN –18% patients (n=18). Eighteen patients were found to have benign disease, 11 patients had low LGPIN, and biopsy was not performed in five patients (Table 3.1).

Table 3.1 Diagnosis for the first 100 patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>50</td>
</tr>
<tr>
<td>HGPIN</td>
<td>18</td>
</tr>
<tr>
<td>LGPIN</td>
<td>11</td>
</tr>
<tr>
<td>Benign</td>
<td>13</td>
</tr>
<tr>
<td>Biopsy not performed</td>
<td>5</td>
</tr>
</tbody>
</table>

3.3.3 Complications

One patient was admitted to hospital for urosepsis requiring IV antibiotic for 2 days. He was subsequently discharged without any further issues. No other complications such as urinary retention or haematuria were reported.
3.3.3 Further management

The majority of patients had treatment plans after their first visit to the OSPC. Table 3.2 demonstrates that 30 patients were booked for re-biopsy, followed by 21 patients booked for radical prostatectomies. Sixteen patients were organised to have active surveillance and 20 were recommended to have follow-up with their GPs. Seven patients underwent radiotherapy, two patients had hormonal therapy, one patient was booked for TURP and litholapaxy, and one patient died of an unknown cause.

Table 3.2 Outcomes following the first visit to the OSPC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of patients (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td>21</td>
</tr>
<tr>
<td>Re-biopsy</td>
<td>30</td>
</tr>
<tr>
<td>Active surveillance</td>
<td>16</td>
</tr>
<tr>
<td>Follow-up by GP</td>
<td>20</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>7</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>2</td>
</tr>
<tr>
<td>TURP and litholapaxy</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>Deceased</td>
<td>1</td>
</tr>
</tbody>
</table>

Almost half of the patients diagnosed with prostate cancer were booked for radical prostatectomy. The median time from referral to surgery was 88.5 days (range 31-308 days). Patients who underwent active surveillance had a Gleason grade 6 (3+3) disease or small focus of disease. Any follow-up appointment and re-biopsy dates were booked and patients were contacted to ensure they were not lost to follow-up. One patient opted to have further discussion and follow-up with his GP for more information prior to specialist follow-up. The two patients with unknown outcomes were informed of their histopathology results and wanted more information prior to committing to treatment.
offered. Table 3.3 summarises the outcome of the 50 patients diagnosed with prostate cancer.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of patients, n=50 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical prostatectomy</td>
<td>21 (42)</td>
</tr>
<tr>
<td>Re-biopsy</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Hormonal treatment</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Follow-up by GP</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

3.4 Discussion

The OSPC model is important in a vast country like Australia where the population is sparsely distributed. This is the first such rapid assessment clinic targeted at public patients, more specifically patients from rural and remote WA, a state where approximately 30% of the population live in rural areas (91). This clinic saves patients numerous unnecessary trips from their home as it aims to investigate and suggest a management plan within one session. A cost analysis for the OSPC at our centre was performed by McCombie et al. (90) for the clinic’s first 200 patients; data included the 100 patients reported in this thesis. It compared the actual travel cost of attending the OSPC to the theoretical cost assessments of patients if standard assessment pathways had been used. The cost calculated was based on the number of return trips to Perth to receive their results and discuss further management, as well as Patient Assisted Travel Scheme
(PATS)-reported travel and accommodation expenses. Cost savings was calculated to be $1045 per person.

As the clinic is targeted to rural WA men, there is still a need to return for a visit at the urologists’ clinic for those found to have prostate cancer. In the near future, we may improve this logistical barrier by adopting video conferencing to discuss ‘face to face’ with a patient their diagnosis of prostate cancer and treatment options (92). It is undeniable that patients would be in a more comfortable environment with the necessary social support during the delivery of diagnosis. Patients would have more time to prepare themselves mentally or be provided with further written information from the rural cancer nurses in the region prior to coming to the metropolitan area for treatment.

The median age group for our patients was 62 years, with our oldest patient being 85. This patient did not have biopsy performed as he was old and frail and a prostate biopsy would not provide additional benefit to his management. Although the clinic has stringent referral criteria on a prepared proforma sent out to country GPs, it does not actually specify an age limit to referral. However, GPs are advised not to refer patients or consult our centre if the patient is compromised by multiple co-morbidities. As the clinic progresses and becomes more popular, modifications to the proforma will need to be made to ensure that appropriate patients are seen in a timely fashion. GPs are also encouraged to seek telephone advice from the urologist who heads the OSPC if they are unsure about referring patients.

About half of our patients seen at the OSPC were found to have prostate cancer, with almost 60% of these diagnosed patients requiring treatment. The high yield of prostate
cancer found in our clinic may be explained by the fact that prostate cancer is the most commonly diagnosed cancer in Australia, accounting for 32.9% of newly diagnosed cancers in male and 18.8% of all newly diagnosed cancers (1). The strict criteria provided to GPs for referral may also explain the high yield of prostate cancer found in our clinic.

The alternatives to a ‘one stop’ healthcare model for men living in rural and remote areas are either the traditional assessment pathway (Figure 3.1) or a visiting urology service. This OSPC model has several advantages over both of these options. The OSPC is a more streamlined healthcare model than traditional assessment pathways; it necessitates only one meeting with a urologist to arrive at a prostate cancer diagnosis as opposed to three. This reduced need to travel to and from a metropolitan centre is highly cost-effective and removes a significant barrier that rural and remote men face in accessing prostate cancer care. The OSPC model also reduces delay from referral to diagnosis compared with traditional assessment pathways (93, 94), with almost seven-fold reduction noted from this study. Although visiting urology services may also confer many of these advantages, the efficiency and reliability of these services is heavily dependent on the regularity of visits and availability of equipment at remote locations. One relative disadvantage of the OSPC model is that it does require a lot of organisational co-ordination, which in our present clinic was performed by the urology nurse (90).

In conclusion, the OSPC is an efficient and effective healthcare model for men living in rural and remote areas of WA suspected of having prostate cancer.
Publication

4. TRUS-guided prostate biopsy: a pain control study

4.1 Introduction

TRUS-guided needle biopsy of the prostate gland has become the gold standard for diagnosing prostate cancer (95). Prostate biopsy is a day procedure and can be performed on an outpatient basis. It is safe and well tolerated by most patients. However, patients still report pain and discomfort during prostate biopsy under local anaesthesia. This can compromise the quality of tissue diagnosis and lead to patients requiring a repeat biopsy under general anaesthesia due to their inability to tolerate the procedure. Studies have shown that about 65-90% of men report discomfort during TRUS-guided biopsy, ranging from mild discomfort to severe pain (97, 98). Almost 19% of patients biopsied without any anaesthesia would refuse re-biopsy again (99).

Studies have shown that periprostatic nerve block (PPNB) with lignocaine is a good and safe form of anaesthesia during the procedure (95, 100-104) and this is routinely used in our unit. Although PPNB with lignocaine is adequate in most patients, some studies have shown that addition of an anti-inflammatory suppository such as diclofenac can decrease the pain experienced during and after prostate biopsy (102, 105). The primary mechanism responsible for its anti-inflammatory, anti-pyretic and analgesic action is inhibition of prostaglandin synthesis by inhibition of cyclo-oxygenase. Diclofenac is available in oral, suppository and injectable forms. The suppository is available in 50 and 100mg forms and it gives effective pain relief for long durations. It is absorbed rapidly and it attains a peak concentration in 30-60 minutes (106). This is useful in the acute use of prostate biopsy and for pain relief post-prostatic biopsy. Published studies involving the use of
combination diclofenac suppository and lignocaine PPNB have also demonstrated that it is safe and effective in reducing pain in prostate biopsy. There was also no significant differences in complications between the two group of patients (102, 105).

Various other methods of analgesia in prostate biopsy have been investigated using lignocaine gel / spray, glyceryl trinitrate ointment, EMLA cream and oral analgesia (paracetamol / codeine). These studies measured the differences in pain scores during and immediately after the biopsy but not pain experienced in the evening or a day after the biopsy. Ragavan et al. (105) reported that many patients complained of significant discomfort after and in the evening of the procedure. This study suggested that the use of diclofenac suppository lowered the evening pain scores in biopsy patients. However, this three-armed study was not placebo-controlled. No study has simply compared lignocaine PPNB alone versus lignocaine PPNB plus diclofenac suppository. In short, this study will examine the potential additional early and late benefits of adding a diclofenac suppository to lignocaine PPNB in a randomised single blind placebo-controlled fashion.

4.2 Patients and methods

A total of 96 patients referred for TRUS prostate biopsy at our centre between August 2011 and August 2012 were included in this study. All patients had been referred to the clinic by their GPs. They will have fulfilled one or more of the following criteria:

- Hard, irregular prostate on DRE.
- Suspicious feeling prostate on DRE – despite normal PSA level for age-specific reference range.
- Raised / rising PSA (age-specific) +/– LUTS.

- Symptoms of prostate cancer and high PSA level.

Exclusion criteria were known allergies to lignocaine or NSAIDs, known gastric or duodenal ulcers, gastrointestinal bleed or perforation, acute / chronic prostatitis, chronic pelvic pain, known recto-anal conditions, previous rectal surgery, and patients currently on warfarin or anti-coagulation therapy. The study was approved by the South Metropolitan Area Health Service human research committee.

Recruited patients were randomised into two groups – combination / treatment analgesia group (diclofenac suppository and lignocaine PPNB) and control group (placebo suppository with lignocaine PPNB). Block randomisation of six was performed using computer software. Enrolled patients gave fully informed consent for both the TRUS prostate biopsy and clinical trial. Either a 100mg diclofenac suppository or a placebo suppository was administered 1 hour prior to the biopsy.

Three clinicians performed the TRUS-guided prostate biopsies at different sessions. In the lateral decubitus position, all patients had DRE performed prior to ultrasound probe insertion. Immediately after the transrectal probe insertion, periprostatic tissue was infiltrated with 10mls of 1% lignocaine hydrochloride injection into the NVBs at the basolateral aspects of the prostate gland. Then measurements of prostatic volume were taken using the same probe. This was followed by 14 core biopsies taken of the prostate gland. Two biopsies were performed for both sides of lateral, base and apex of the gland. Two additional biopsies of the TZs were performed, one from each side. All tissue samples were labelled and sent to the pathology lab for further analysis. Patients were
observed for at least an hour after the procedure and were discharged home if they voided successfully or had no immediate complications.

Pain scores were recorded using the Numerical Rating Scale (NRS) for pain by the primary researcher. Pain scores ranged from 0-10, with 0 corresponding to no pain, no discomfort and 10 corresponding to maximal pain or discomfort. Pain scores were collected from all patients at these time periods:

- Pain / discomfort experienced from introduction and presence of probe.
- Biopsy (pain felt from needle)
- Pain experienced 1 hour after biopsy
- Pain later that evening
- Pain 1 day after biopsy

Patients received a telephone follow-up a day after the biopsy by the researcher or research nurse to obtain the pain scores post-discharge. Questions related to potential side effects experienced were also asked. All patients were advised to call or return to our centre if unexpected side effects occurred. This allowed for recording of potential complications that occurred several days after the biopsy.

SPSS v19 was used to analyse the data by an independent statistician. The pain scale score is an interval score and was treated as parametric data. ANOVA tests were used to examine differences between treatment groups with respect to age, PSA and pain scores at five time points: Time 1 – probe insertion, Time 2 – biopsy, Time 3 – 1 hour after biopsy, Time 4 – 6pm and Time 5 – 1 day post biopsy. ANOVAs were also used to test
for differences between clinics and pain scale scores. A Chi-Square test was used to test for differences between groups with respect to a repeat biopsy.

4.3 Results

A total of 97 patients were eligible and recruited for the trial. One patient eligible for the trial did not sign the written consent and was unable to continue further. Table 4.1 demonstrates the baseline characteristics of the patients. There were no significant differences in age (F=0.203, p=0.653) and PSA (F=0.301, p=0.584) between treatment groups.

Table 4.1 Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=48)</th>
<th>Placebo (n=48)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.2</td>
<td>8.1</td>
<td>63.0</td>
</tr>
<tr>
<td>PSA (ng/dl)</td>
<td>9.6</td>
<td>10.2</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Table 4.2 shows the pain scores experienced by patients at the various time periods, from probe insertion to a day post-biopsy. Table 4.3 includes the number of patients who would agree to have repeat TRUS-guided prostate biopsy under local anaesthesia. There were no significant differences in age (F=0.203, p=0.653) and PSA (F=0.301, p=0.584) between treatment groups. The placebo pain scores were on average higher than the treatment pain scores at Times 3 and 4. The differences in pain scores between treatment and placebo were not significant at Time 1 (F=1.089, p=0.299), Time 2 (F=0.000, p=0.983), Time 4 (F=1.455, p=0.231) and Time 5 (F=0.764, p=0.384). At Time 3, the
pain scores were significantly higher in the placebo group than the treatment group’s pain scores \( (F=4.188, \ p=0.044) \).

**Table 4.2  Pain scores at various time periods**

<table>
<thead>
<tr>
<th>Pain scale</th>
<th>Treatment (n=48)</th>
<th>Placebo (n=48)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Time 1 – probe insertion</td>
<td>3.92</td>
<td>2.53</td>
<td>3.44</td>
</tr>
<tr>
<td>Time 2 – biopsy</td>
<td>4.49</td>
<td>2.47</td>
<td>4.48</td>
</tr>
<tr>
<td>Time 3 – 1 hour after biopsy</td>
<td>1.13</td>
<td>1.19</td>
<td>1.75</td>
</tr>
<tr>
<td>Time 4 – 6pm</td>
<td>0.94</td>
<td>1.39</td>
<td>1.33</td>
</tr>
<tr>
<td>Time 5 – 1 day post biopsy</td>
<td>0.47</td>
<td>1.00</td>
<td>0.31</td>
</tr>
</tbody>
</table>

**Table 4.3  Number of patients who underwent repeat biopsy under local anaesthesia**

<table>
<thead>
<tr>
<th>Repeat biopsy under local anaesthesia</th>
<th>n</th>
<th>%</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>41</td>
<td>87.2</td>
<td>37</td>
<td>80.4</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>12.8</td>
<td>9</td>
<td>19.6</td>
</tr>
</tbody>
</table>

There was no significant difference between treatment (87%) and placebo (80%) groups with respect to whether they would prefer to repeat the biopsy under local anaesthetic \( (X^2=0.794, \ p=0.373) \). One patient from the placebo group was admitted with urosepsis post-biopsy and two patients from the treatment group had urinary tract infections requiring a course of oral antibiotics. No other reported post-biopsy complications were found in the other patients.

### 4.4 Discussion

TRUS-guided biopsy of the prostate is the current standard test for diagnosis of prostate cancer and was introduced into clinical practice in Australia in 1989. The method of pain control used is either IV sedation or PPNB using a local anaesthetic agent such as 1% lignocaine, depending on clinician preference. The prostate gland’s nerve supply is
autonomic and originates from the inferior hypogastric plexus adjacent to the seminal vesicles. The prostatic plexus courses with the prostatic vascular structures as the NVB at the posterolateral border of the prostate. These posterolateral fibres are thought to be the main nerve supply of the prostate since only a few nerve fibres are situated on the superolateral and anterior surfaces of the prostate (2). PPNB should provide adequate analgesia as the technique infiltrates these nerves.

A literature search was undertaken of use of various analgesia, specifically diclofenac suppository in TRUS prostate biopsy using the search terms diclofenac; suppository; analgesia AND prostate biopsy to explore what evidence was available to support the use of additional agents to assist pain control in addition to using a PPNB.

Lee et al. (107) described improved patient tolerance of using this technique to help obtain core biopsies, as employing an automatic firing device made the procedure swifter. Furthermore, tolerance was aided by the site of the biopsy – the rectal wall is relatively insensitive in comparison to a transperineal approach. Although there is no consensus on the ideal number of core prostate biopsies that should be performed, current practice recommends at least eight core biopsies. The traditional sextant biopsies yielded high false negative error rates of 20-30% (108). An increased numbers of core biopsies up to 14 cores may subject patient to more discomfort or pain during the procedure. Therefore, our study aimed to find out if the administration of a simple anti-inflammatory suppository reduced any pain or discomfort felt during or after the procedure.

Studies by Nash et al. (109) employing PPNB techniques using 1% lignocaine have proven that patients’ tolerability of this diagnostic test can be further improved – up to
19% of patients would refuse re-biopsy if no anaesthesia was administered (99). Further, although PPNB with lignocaine is adequate in most patients, it has been shown that addition of an anti-inflammatory suppository such as diclofenac can decrease pain experienced during and after prostate biopsy (102, 105). Published studies involving the use of combination diclofenac suppository and lignocaine PPNB have also demonstrated that it is safe and effective in reducing pain in prostate biopsy. There were also no significant differences in complications between the two groups of patients (102, 105).

Ragavan et al. (105) reported that many patients complained of significant discomfort after and in the evening of the procedure. This study suggested that the use of diclofenac suppository lowered the evening pain scores in biopsy patients; however, it was a three-armed study that was not placebo-controlled. Haq et al. (110) found that a diclofenac suppository given an hour before prostate biopsy decreased pain experienced during the biopsy without significant increase in morbidity.

The diclofenac suppository is favoured over the oral form of the drug for treatment of acute pain in the emergency setting such as renal or biliary colic. Diclofenac belongs to the phenylacetic acid derivatives and is an anti-inflammatory, specifically inhibiting the enzyme cyclo-oxygenase which works both locally and systemically (111, 112). The primary mechanism responsible for its anti-inflammatory, anti-pyretic and analgesic action is inhibition of prostaglandin synthesis. It is absorbed rapidly and it attains a peak concentration in 30-60 minutes (106). This is useful in the acute use of prostate biopsy and for pain relief post-prostatic biopsy. This can be compared to oral diclofenac which can vary from 30 minutes to 21.5 hours (106). Therefore, the suppository form was the
chosen analgesia of choice for this study. Our study has shown a small reduction of pain reported at 1 hour post-biopsy – 1.75 versus 1.13; however, it is probably not enough to be of clinical relevance or to justify the costs, risks and potential harms (unmeasured given the small size of the study) of the intervention. A reduction in pain score on the Numerical Rating Scale of approximately 2 points represents a clinically important difference (113).

Various other methods of analgesia in prostate biopsy have been investigated using lignocaine gel / spray, glyceryl trinitrate ointment, EMLA cream and oral analgesia (paracetamol / codeine). These studies measured the differences in pain scores during and immediately after the biopsy but not pain experienced in the evening or a day after the biopsy (114-119).

Studies which used topical glyceryl trinitrate as an adjunct to 1% lignocaine PPNB yielded significantly lower pain scores during probe insertion and less overall discomfort during the procedure (116, 117). Another topical analgesia, lignocaine gel, has also been trialled in several other studies and when used alone has not demonstrated a decrease in pain during prostate biopsy (115, 120, 121). The majority of studies concluded that the use of lignocaine / lidocaine PPNB alone does decrease pain during the biopsy – this concurs with our study findings (95, 100, 101, 114, 115, 121).

Other modalities of non-invasive imaging technique such as MRI may help in reducing the need for prostate biopsies in low-risk patients and hence prevent pain otherwise present in prostate biopsies. MRI has the ability to detect higher grade and volume prostate tumours and therefore prevent unnecessary prostate biopsies for insignificant
tumours (122). It can also help in targeting prostate biopsy for patients undergoing active surveillance and reduce the number of core biopsies required. Therefore, MRI may be a useful, non-invasive method to consider in some patients having to undergo further investigation or surveillance of prostate cancer as it can reduce or prevent pain.

The post-biopsy complication rates reported between both groups in our studies were almost equal – one placebo group patient was admitted for urosepsis whilst two patients in the treatment group had urinary tract infections. Two out of the three patients had diabetes which may have predisposed them to higher rates of infection. Although our numbers were small, our overall complication rate was 3.13% which fits with previously quoted 0.1-2.4% complication rates in other studies (123). No direct side effects were reported from the diclofenac suppository administered.

Although the number of patients recruited was enough to power the study, the majority of patients in our study were rural patients. This may account as one of the limitations in our study as non-metropolitan patients are often thought of as having different health attitudes, including stoicism (84, 124). As such, our results may not reflect pain perception of a bigger cohort of patients undergoing TRUS-guided prostate biopsies in WA. Other sources of potential bias are different operators, sampling patterns and duration of the biopsies not measured in our study. As such, there may have been a difference that our study did not detect due to the presence of such bias.

Our study did not demonstrate that using additional diclofenac suppository in addition to PPNB for prostate biopsy resulted in a clinically significant reduction in pain or improve tolerability of the procedure. PPNB is extremely well tolerated in TRUS-guided prostate
biopsy as the vast majority of our patients would elect to have repeat prostate biopsies under local anaesthesia. Alternative additional analgesic options may deserve consideration.
Chapter 5
5. **General discussion**

5.1 **Major conclusions of this thesis**

Through literature review and original contemporary findings, this thesis has presented clear evidence for inequalities in the access to prostate cancer diagnostics and subsequent treatment, both in WA and nationally. The reduced access of rural patients to cancer diagnostics may be a significant problem, ultimately leading to delayed presentation and poorer outcomes for patients.

Improved access to TRUS biopsies through innovations such as an OSPC will help to address this issue. The OSPC model relies on prostate biopsy using local anaesthetic. Improving the tolerability of this procedure is an important clinical issue. The randomised trial reported in this thesis found that local anaesthetic TRUS-guided prostate biopsy is well tolerated and has few complications. It has also answered an important clinical question – the lack of benefit from addition of a diclofenac suppository. Further research aimed at improving the tolerability of TRUS biopsy is warranted.

5.2 **Clinical impact**

There is potential for the role of MRI to be extended. During the course of this thesis work, MRI has become more prominent in the assessment of patients with prostate cancer. When dealing with rural and remote patients, OSPC now uses an MRI scan of the prostate at the initial assessment. This radiological modality allows cognitive targeting of suspicious areas by the urologist performing the TRUS biopsy. It has the additional
benefit of being able to exclude serious lesions when present in the anterior zone of the prostate, which is difficult to access transrectally.

Data from this thesis was used to support a successful grant application by the Australian and New Zealand Urogenital and Prostate (ANZUP) group to Cancer Australia. This funding was for a national multi-centre, randomised controlled trial to investigate a novel addition to periprostatic local anaesthetic infiltration (PILA). The Pain Free TRUS B trial (Trial Registration Number ACTRN12615001105538) is now open in Australia and the first centre was at the Fiona Stanley Hospital in Perth, WA.

The hypothesis of this trial was that addition of methoxyflurane (Penthrox®) to periprostatic infiltration of local anaesthesia has positive effects on the pain level and discomfort that is traditionally experienced by patients undergoing a TRUS prostate biopsy. The trial will also examine the safety of methoxyflurane (Penthrox) in patients who undergo local anaesthetic TRUS prostate biopsy.

The target population for the trial is men who are scheduled to undergo their first TRUS biopsy of the prostate for elevated PSA or for abnormal DRE. Participants are randomised 1:1 to inhaled methoxyflurane or placebo and stratified by age and study site. All participants are treated with PILA (2% lignocaine), injected into and around the prostate prior to the biopsy. The primary objective is to determine the effects of inhaled methoxyflurane on pain rated by participants 15 minutes post-biopsy. Secondary endpoints include other aspects of the biopsy experience as rated by the participants, including their willingness to undergo a future biopsy. Other secondary endpoints include the urologist’s rating of the participant’s biopsy experience, biopsy completion, frequency
of specified adverse events and frequency of hospitalisation. A sample size of 420 men provides >85% power at the two-sided, 5% level of significance to detect a 0.80 point difference in mean pain scores (on a scale of 0-10), assuming a standard deviation of 2.5 and allowing for missing data. Patients will complete a questionnaire to document their experience of the biopsy at 15-30 minutes post-biopsy and at 7-35 days after the procedure. Urologists will complete a questionnaire on the day of the procedure (125).
6. References


127. Radiology ACo. PI-RADS v22015.


7. Appendices

7.1 Appendix 1

**FREMANTLE HOSPITAL “ONE STOP PROSTATE CLINIC”**

- New weekly clinic (Tuesday mornings/afternoons) to be held at Kaleeya Hospital.
- GPs can refer patients with clinical suspicion of prostate cancer to this clinic.
- Patients will be assessed by a consultant urologist & if suitable, a **TRUS prostate biopsy will be performed on the same day** under local anaesthesia. Please warn patients that they would most likely have the biopsy performed on the day of the clinic.
- **Objective of the clinic:**
  - Expedite referrals for patients who potentially need a TRUS prostate biopsy.
  - Country patients will be saved many trips to Perth for follow-ups. If biopsy results are negative, patient will have telephonic follow-up of results by Urology Research Nurse/Urology Fellow and will be discharged without further need for another trip to Perth. If results are positive/equivocal, patients will have Urology follow-up arranged to have further discussion about management plan.
- Please use proforma attached when referring the patients to the “One Stop Prostate Clinic”. Ensure that a named referral is sent, i.e. tick a consultant’s name.
- Please advise patients to **withhold warfarin/clopidogrel 10 days** prior to clinic appointment.
- Further patient info sheet about the TRUS prostate biopsy will be sent out to patients when their clinic dates are confirmed.
REFERRAL FORM:
FREMANTLE HOSPITAL ONE STOP PROSTATE ASSESSMENT CLINIC

This proforma for the One Stop Prostate Assessment Clinic at Fremantle Hospital aims to ensure that patients are seen urgently with the appropriate and necessary investigations prior to being seen by consultant urologists.

Referral to urologist (please tick):
☐ Prof. D. Hayne

Please ensure that referrals are made out to: “One Stop Prostate Clinic”. Fax: 08-9431 2009

Patient name:
Date of birth:
Age:
Address
Telephone no:
Mobile no:
Medicare no:
Patient’s weight (kgs):

GP name:
Practice address:
Practice telephone number: Practice fax number:

<table>
<thead>
<tr>
<th>PSA Readings:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st reading:</td>
<td></td>
</tr>
<tr>
<td>2nd reading:</td>
<td></td>
</tr>
</tbody>
</table>

- 2 PSA readings must be included in referral.

At least one of the below criteria is to be met for referral to the clinic:

- Hard, irregular prostate on digital rectal exam (DRE)
- Suspicious feeling prostate on DRE (even with normal PSA for age-specific reference range)
- Raised/rising PSA(age-specific) +/- lower urinary tract symptoms
- With symptoms and high PSA levels

[An urgent referral is not needed if the prostate is simply enlarged and the PSA is in the age-specific reference range.]
[If PSA is tested during an episode of urinary tract infection it will likely be elevated. PSA testing should be deferred until or repeated after appropriate antibiotic treatment.]

[In patients compromised by other co morbidities, discussion with the patient or carers and/or a specialist may be more appropriate]

PAST MEDICAL HISTORY:

FAMILY HISTORY:

SOCIAL HISTORY:

CURRENT MEDICATIONS:
• Anti-coagulants:
• Clopidogrel
• Warfarin
• Aspirin
• Asasantin
• Others (please list):

TRUS biopsies cannot be safely performed on anti-coagulated patients. Warfarin and clopidogrel should be withheld for 10 days prior to “One Stop Prostate Clinic” appointment.

ALLERGIES:

PHYSICAL EXAMINATION:

Please attach other pathology results or imaging results to the referral:

Modified on 6th May 2012
7.3 Appendix 3

INFORMATION SHEET
TO BE USED IN CONJUCTION WITH THE CONSENT FORM
A randomised controlled trial comparing use of lignocaine periprostatic nerve block alone and combination diclofenac suppository with lignocaine periprostatic nerve block for patients undergoing transrectal ultrasound guided biopsy of prostate.

We invite you to participate in a clinical research study where patients having prostate biopsy will be given an additional painkiller (diclofenac suppository). The local sponsor at this site is the Urology Department, Fremantle Hospital. This study has been approved by the South Metropolitan Area Health Service Human Research Ethics Committee.

If you decide to take part in this research study, it is important that you understand the purpose of the study and the procedures you will be asked to undergo. Please read the following pages, which will provide you with information about the treatments involved, and also the potential benefits, discomforts and precautions of the study. If you are currently involved in a research study you will be ineligible to participate in this one.

For some of you, this will be the first time you have been told about transrectal ultrasound-guided (TRUS) prostate biopsy. There is an additional informational sheet attached about TRUS prostate biopsy which you may find helpful.

Nature and Purpose of the Study
We have asked you to participate in this study as you have been referred for a TRUS prostate biopsy. This is a procedure that is conducted to diagnose potential prostate cancer. It is important to understand that not all patients who undergo prostate biopsy will be diagnosed with prostate cancer.

Commonly patients who undergo TRUS prostate biopsy will have local anaesthetic injected into the area of biopsy. This will help prevent any pain or discomfort you may feel during the procedure. We propose also using a diclofenac suppository (anti-inflammatory) an hour before your procedure. Patients suitable for the study will be chosen at random to receive a diclofenac suppository or placebo (substance containing no medication) suppository. Therefore, there is a chance you may not receive the medicated suppository.

Although the standard practice of administering local anaesthetic injection is sufficient for some patients, it is not known whether the addition of the diclofenac suppository is effective in reducing pain during or after the biopsy. Therefore, this study aims to find out if additional anti-inflammatory given before the biopsy will truly reduce pain during and after the biopsy. If there is a proven benefit in giving an anti-inflammatory before the procedure, this can be given in the future to make the biopsy more comfortable for patients.
What the Study Will Involve

If you decide to participate in this study, you will receive a suppository and the local anaesthetic injection (as planned) before your TRUS prostate biopsy. The suppository will be given an hour before your biopsy to ensure that the medication has time to work. You could either be receiving a diclofenac suppository or a placebo suppository. You will be randomly chosen to have either the anti-inflammatory or placebo suppository. A computerised random generator will decide the suppository you receive without any bias. Your nurse will assess you to ensure you will be suitable for the study. If you have the following conditions, you will unfortunately not be eligible for the study:

- Known allergies to lignocaine or anti-inflammatories.
- Acute/chronic prostatitis.
- Chronic pelvic pain
- Known conditions in the rectum or anus.
- Previous surgery in the rectum or anus.
- On warfarin/clopidogrel.

A nurse or doctor will ask you to complete a questionnaire that records your pain score during and after the procedure. This questionnaire will take approximately 1-2 minutes to complete. You will also receive telephone follow-up from a research Urology nurse/doctor to find out if there was any further pain in the evening and a day after the procedure. They will also ask if you experienced any side-effects from the medication and complications after the procedure. There may be more than one telephone call made to complete the data collection for the study and to ensure that you are well. Each telephone call will be approximately 5 minutes in duration.

Follow Up

You will have your routine follow-up as planned by your urologist. Any unusual reactions not expected from the study will be reported directly to medical staff and necessary treatment or further investigations will be performed.

Benefits

A potential benefit of participating in this study is that the use of both diclofenac suppositories and local anaesthetic injection will significantly reduce pain during and after prostate biopsy. However, it is possible that there may be no direct benefit to you from participation in this study. While there is no guarantee that you will benefit, the knowledge gained from your participation may help others in the future.
Discomforts and Risks

The trials already conducted have shown this combination of painkillers to be very safe. However, there is a risk of developing potential complications from the prostate biopsy including blood in the urine, inability to pass urine and urine tract infection. This is why we will be checking for the above symptoms regularly. If at any time you appear to develop a more serious side effect such as sepsis (infection in the bloodstream), please seek immediate medical attention at your closest hospital.

Voluntary Participation and Withdrawal from Study

Participating in this trial will not in any way interfere with your procedure or potential treatments. Your Doctors in the Urology Department will perform the TRUS prostate biopsy in the standard manner.

Your participation in this study is entirely voluntary. If you decide not to participate in this study, your prostate biopsy will be performed according to routine clinical guidelines, without any prejudice to present or future management in this hospital.

You may withdraw from this study at any time, for whatever reason. Such withdrawal will not in any way influence decisions regarding future standard or conventional medical treatment you may require.

If you should have any complaints or concerns about the way in which the study is being conducted, you may contact the Chairman of the South Metropolitan Area Health Service Human Research Ethics Committee on 9431 2929.

For further questions regarding the study, please contact:

Dr. Wei Ling Ooi, Urology Research Fellow
Tel: 08-9431 3333 (switchboard Fremantle Hospital)
The future of prostate imaging and biopsy

Use of MRI in prostate cancer

MRI was first reported visualising prostate cancer in 1983 by Hricak et al. (126). The authors concluded that the higher intensity signal allowed the differentiation of malignant prostate tissue from benign tissues. In the initial stage of MRI scanning of the prostate, morphologic assessment of the gland was solely based on T1-weighted (T1W) and T2-weighted (T2W) pulse sequences. It was found to be most useful in loco-regional staging of biopsy-proven prostate cancer. However, early prostate MRI was found to be limited in terms of distinguishing between benign and pathological tissues and identifying clinically insignificant prostate cancer.

With advances in technology, modern day multi-parametric MRI was developed. It combines anatomic T2W with functional and physiologic assessment including diffusion-weighted imaging (DWI) and its derivative apparent diffusion coefficient (ADC) maps, dynamic contrast enhanced (DCE) MRI and sometimes other techniques such as in-vivo MR proton spectroscopy (127). Multi-parametric MRI has improved the clinicians’ ability to detect clinically significant prostate cancer and be able to differentiate benign disease and clinically insignificant prostate cancer from those that are clinically significant. A study has reported that men who had prior negative biopsies and persistently elevated PSA levels were found to have better detection of malignancy using this technique compared to conventional USS guidance (128). The detection rate of cancer was 41% for the MRI-guided group compared to 18% in the USS-guided group in this series.

MRI prostate has also expanded its use to include tumour detection, localisation, characterisation, risk stratification, surveillance, assessment of suspected recurrence and image guidance for biopsy, surgery, focal therapy and radiation therapy (127).

Prostate Imaging Reporting and Data System (PI-RADS)

In 2012, the European Society of Urogenital Radiology (ESUR) created a scoring system known as the Prostate Imaging Reporting and Data System (PI-RADS). This exists for multi-parametric MRI used in the detection of prostate cancer. This scoring system provides standardisation and consistency in the interpretation of MRI prostate in various centres. Since publication, the PI-RADS score has been validated in various clinical and research scenarios. To further ensure global standardisation of PI-RADS, a committee – which included ESUR, the American College of Radiology (ACR) and AdMeTech Foundation – developed a more updated and improved guideline for PI-RADS, now known as PI-RADS v2. According to guidelines published by the ACR, the aims of PI-RADS is to:
- Establish minimum acceptable technical parameters for prostate MRI.
- Simplify and standardise the terminology and content of radiology reports.
- Facilitate the use of MRI data for targeted biopsy.
- Develop assessment categories that summarise levels of suspicion or risk and can be used to select patients for biopsies and management (e.g. observation versus immediate intervention).
- Enable data collection and outcome monitoring.
- Educate radiologists on prostate MRI reporting and reduce variability in imaging interpretation.
- Enhance interdisciplinary communications with referring clinicians.

The PIRADS reporting system defines clinically significant prostate cancer as:

- Pathology / histology as Gleason score ≥7 (including 3+4 with prominent but not predominant Gleason 4 component)

and/or

- Volume ≥0.5cc

and/or

- Extra prostatic extension

PI-RADS uses a 5-point scale based on probability that a combination of MRI prostate findings on T2W, DWI and DCE correlates with the presence of a clinically significant cancer for each lesion in the prostate gland (127). It is divided into these categories:

- PI-RADS 1: Very low (clinically significant cancer is highly unlikely to be present).
- PI-RADS 2: Low (clinically significant cancer is unlikely to be present).
- PI-RADS 3: Intermediate (the presence of clinically significant cancer is equivocal).
- PI-RADS 4: High (clinically significant cancer is likely to be present).
- PI-RADS 5: Very high (clinically significant cancer is highly likely to be present).

Tables A1 and A2 summarise PI-RADS
Table A1  Data from the Peripheral zone (PZ)

<table>
<thead>
<tr>
<th>DWI</th>
<th>T2W</th>
<th>DCE</th>
<th>PI-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Any</td>
<td>Any</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Any</td>
<td>Any</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>Any</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>Any</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Any</td>
<td>Any</td>
<td>5</td>
</tr>
</tbody>
</table>

Table A2  Data from the Transition zone (TZ)

<table>
<thead>
<tr>
<th>T2W</th>
<th>DWI</th>
<th>DCE</th>
<th>PI-RADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Any</td>
<td>Any</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Any</td>
<td>Any</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>≤4</td>
<td>Any</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Any</td>
<td>Any</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>Any</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Any</td>
<td>Any</td>
<td>5</td>
</tr>
</tbody>
</table>

T2W images are useful in distinguishing prostatic zonal anatomy, assessing abnormalities within the gland, and evaluating seminal vesicle invasion, extra-prostatic extension and nodal involvement. If a clinically significant cancer is seen in the PZ of T2W images, it would usually appear round or as an ill-defined hypointense focal lesion. However, other conditions such as prostatitis, haemorrhage, glandular atrophy, benign hyperplasia, biopsy-related scars or therapy to the prostate itself (e.g. hormone, ablation) can also give such appearances (127). In the TZ, tumours would be seen as non-circumscribed homogenous, moderately hypointense lesions (of ‘erased charcoal’ or ‘smudgy fingerprint’ appearance). Other features which would make it a clinically significant cancer would include spiculated margins, lenticular shape, absence of complete hypointense capsule, invasion of the urethral sphincter or AFS.

The following tables, as adopted from the most current guidelines by the ACR for the PI-RADS v2, give a summary of the PI-RADS v2 score for assessment of T2W (Tables A3 & A4).
Table A3  PI-RADS v2 assessment of T2W: scores for the PZ

<table>
<thead>
<tr>
<th>Score</th>
<th>PZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Uniform hyperintense signal intensity (normal)</td>
</tr>
<tr>
<td>2</td>
<td>Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin</td>
</tr>
<tr>
<td>3</td>
<td>Heterogenous signal intensity or non-circumscribed, rounded, moderately hypointensity. Includes others that do not qualify as 2, 4 or 5</td>
</tr>
<tr>
<td>4</td>
<td>Circumscribed, homogenous moderate hypointense focus / mass confined to prostate and &lt;1.5cm in greatest dimension</td>
</tr>
<tr>
<td>5</td>
<td>Same as 4 but ≥1.5cm in greatest dimension or definite extra prostatic extension / invasion behaviour</td>
</tr>
</tbody>
</table>

Table A4  PI-RADS v2 assessment of T2W: scores for the TZ

<table>
<thead>
<tr>
<th>Score</th>
<th>TZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Homogenous intermediate signal intensity (normal)</td>
</tr>
<tr>
<td>2</td>
<td>Circumscribed hypointense or heterogenous encapsulated nodule(s) (BPH)</td>
</tr>
<tr>
<td>3</td>
<td>Heterogenous signal intensity with obscured margins</td>
</tr>
<tr>
<td></td>
<td>Include others that do not quality as 2, 4 or 5</td>
</tr>
<tr>
<td>4</td>
<td>Lenticular or non-circumscribed, homogenous, moderately hypointense and &lt;1.5cm in greatest dimension</td>
</tr>
<tr>
<td>5</td>
<td>Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension / invasive behaviour</td>
</tr>
</tbody>
</table>

DWI reflects random motion of water molecules and is a key component to prostate MRI exam. It should include ADC map and high b-value images. ADC map is a display of ADC values for each voxel in an image. Most clinically significant cancers have restricted or impeded diffusion compared to normal tissues. They appear hypointense on grey-scale ADC maps. High b-value images display preservation of signal in areas of restricted or impeded diffusion compared with normal tissues which demonstrate diminished signals. Table A5 summarises the PI-RADS v2 assessment of DWI.
Table A5    PI-RADS v2 assessment of DWI: scores for the PZ and the TZ

<table>
<thead>
<tr>
<th>Score</th>
<th>PZ or TZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No abnormality on ADC and high b-value DWI</td>
</tr>
<tr>
<td>2</td>
<td>Indistinct hypointense on ADC</td>
</tr>
<tr>
<td>3</td>
<td>Focal mildly or moderately hypointense on ADC and isointense / mildly</td>
</tr>
<tr>
<td></td>
<td>hyperintense on high b-value DWI</td>
</tr>
<tr>
<td>4</td>
<td>Focal markedly hypointense on ADC and markedly hyperintense on high b-</td>
</tr>
<tr>
<td></td>
<td>value DWI; &lt;1.5 cm in greatest dimension</td>
</tr>
<tr>
<td>5</td>
<td>Same as 4 but ≥1.5 cm in greatest dimension or definite extraprostatic</td>
</tr>
<tr>
<td></td>
<td>extension or invasive behaviour</td>
</tr>
</tbody>
</table>

DCE MRI is the acquisition of rapid T1W gradient echo scans before, during and after the intravenous injection of a low molecular weight gadolinium-based contrast agent. Prostate cancers demonstrate early enhancement following the injection of the above agent. Table A6 summarises the recommended scoring assessment by PI-RADS v2 for DCE.

Table A6    PI-RADS v2 assessment of DCE: scores for the PZ and the TZ

<table>
<thead>
<tr>
<th>Score</th>
<th>PZ or TZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>(–)</td>
<td>No early enhancement or diffuse enhancement not corresponding to a</td>
</tr>
<tr>
<td></td>
<td>focal finding on T2 and / or DWI or focal enhancement corresponding to a</td>
</tr>
<tr>
<td></td>
<td>lesion demonstrating features of BPH on T2WI</td>
</tr>
<tr>
<td>(+)</td>
<td>Focal and earlier than or contemporaneously with enhancement of</td>
</tr>
<tr>
<td></td>
<td>adjacent normal prostatic tissues and corresponds to suspicious findings</td>
</tr>
<tr>
<td></td>
<td>on T2W and / or DWI</td>
</tr>
</tbody>
</table>

According to the ACR (127), the PI-RADS v2 assessment category should be based on prostate MRI findings only and should not incorporate other factors such as PSA, DRE, clinical history or choice of treatment. Prostate biopsy should be considered for PI-RADS 4 and 5 but not for PI-RADS 1 and 2. For PI-RADS 2 and 3, the choice of proceeding with a biopsy is not only dependent on prostate MRI findings alone; other factors, as listed above, may need to be taken into account.

DCE plays a minor role in deciding PI-RADS assessment category if T2W and DWI are of diagnostic quality. Absence of early enhancement within a lesion usually adds little information, and diffuse enhancement not localised to a specific T2W or DWI abnormality can be seen in the setting of prostatitis (127). DCE does not add to the overall assessment when the findings are under the low (PI-RADS 1 or 2) or high (PI-RADS 4 or 5) likelihood of clinically significant cancer. Conversely, when DWI is PI-RADS 3 in the
PZ, a positive DCE may increase the chance of clinically significant cancer and may upgrade the PI-RADS assessment category to 4.

In terms of reporting, in conjunction with the PI-RADS assessment category, the ACR recommends that the following three aspects should be included in the reporting of the prostate MRI – measurement of the prostate gland, mapping lesions, and measurement of lesions.

**Measurement of the prostate gland:** The volume of the prostate gland must be included in the report. It can be determined either via manual or automated segmentation or calculated using the formula for a conventional prolate ellipse:

\[(\text{maximum AP diameter}) \times (\text{maximum transverse diameter}) \times (\text{maximum longitudinal diameter}) \times 0.52.\]

**Mapping lesions:** In order to map lesions, the PI-RADS assessment uses 39 sectors / regions (127) – 36 for the prostate, two for the seminal vesicles and one for the external urethral sphincter. The prostate is divided into right and left on axial sections by a vertical line drawn through the centre, indicated by the prostatic urethra. It is further divided into anterior and posterior by a horizontal line through the middle of the gland. The right and left PZ at prostate base, mid-gland and apex are each subdivided into three sections – anterior, medial posterior and lateral posterior. The right and left TZ at prostate base, mid-gland and apex are each subdivided into two sections – anterior and posterior. The CZ is included in the prostate base around the ejaculatory ducts. The AFS is divided into right and left at the prostate base, mid-gland and apex. The seminal vesicles are divided into right and left. The urethral sphincter is marked in the prostate apex.

Up to four findings with PIRADS Assessment Category 3, 4 or 5 may each be assigned on the sector map and the index (dominant or the lesion with the highest PI-RADS assessment category) intraprostatic lesion should be identified. If more than two lesions are assigned the highest PI-RADS assessment category, the index lesion should be the one that shows extraprostatic extension regardless of the size of the lesion. If none of the lesions demonstrate extraprostatic lesion, the one with the highest PI-RADS assessment category should be considered the index lesion. If more than four suspicious findings are present, the four with the highest likelihood of clinically significant cancer should be reported. It is optional to report additional findings with PIRADS Assessment Category 2 or definitely benign findings. These benign findings may assist as landmarks to guide subsequent biopsy or for tracking lesions in subsequent MRI exams.

**Measurement of lesions:** The minimum requirement is to report the largest dimension of a suspicious finding on an axial image. If the largest dimension is on sagittal / coronal images, the measurement and images should be reported as such. The volume of the
lesion can also be reported. In the PZ, lesions should be measured on ADC whilst, in the TZ, lesions should be measured on T2W.

**MRI-guided prostate biopsy**

Three methods of MRI-guided prostate biopsy are known – cognitive fusion, direct MRI-guided biopsy, and software co-registration of stored MRI with real-time USS (129). Cognitive fusion involves the USS operator aiming the biopsy needle at the prostate area where the lesion is demonstrated on MRI. A review by Moore et al. (130) demonstrated that cognitive fusion does yield improved accuracy over conventional systematic, blind biopsy.

Direct MRI-guided biopsy, commonly known as MRI in-bore biopsy is performed within an MRI tube by a radiologist who fuses a previous MRI demonstrating the lesion with a current MRI to confirm needle localisation (129). The biopsy is performed via a transrectal route and only a few targeted core biopsies are taken. After each biopsy sample, the patient is rescanned to confirm localisation. Unlike conventional USS-guided biopsies, systematic extended core biopsies are not taken. This provides the advantage of limited number of cores and exact localisation of biopsy with reduction in detecting insignificant cancers. The disadvantage of this method includes cost and time required for the procedure and the fact that patients require two MRI scanning sessions.

MRI-targeted biopsy has a role in providing detection of clinically significant prostate cancer with less biopsies required. A recent published study by Siddiqui et al. (131) demonstrated that targeted MRI biopsy diagnosed 30% more high-risk cancers compared to standard biopsy (173 versus 122 cases) and 17% fewer low-risk cancers (213 versus 258 cases). Targeted biopsy also had better predictive ability when compared to standard biopsy for differentiating low-risk from intermediate- and high-risk disease in 170 men after pathology obtained following prostatectomy.

**Management of localised prostate cancer**

Treatment for men with localised prostate cancer is tailored to the individual patient’s circumstance such as preceding urinary and sexual function, life expectancy, co-morbidities and the patient’s individual preferences. Due to the anatomical location of the prostate, treatment-related morbidity is a crucial factor when determining the choice of specific treatment modality. The following three options are possible treatment options available to men diagnosed with localised prostate cancer – no initial treatment (active surveillance or watchful waiting), surgery (radical prostatectomy) or radiotherapy.

*Active surveillance or watchful waiting*

The term ‘active surveillance’ implies that patients diagnosed with prostate cancer would be carefully monitored but currently would not necessarily benefit from treatment. The
main purpose of providing active surveillance to certain groups of patients is to reduce the risk of treatment-related complications for certain types of cancer not likely to progress. Prior to commencing active surveillance, patients are also forewarned of the risk of disease progression or metastasis, of the need for increased regular visits and tests, and that subsequent treatments would need to be more aggressive (17). If there is disease progression, patients under the category of active surveillance would be recommended treatment. ‘Watchful waiting’ is the deferment of palliative intent treatment – usually on development of bony metastases.

Although there are many differing opinions about active surveillance criteria, the following are criteria recommended by National Comprehensive Cancer Network (NCCN) (132). Patients suitable for active surveillance are those who (17) have low-risk prostate cancer (T1-T2a and Gleason 2-6 and PSA<10ng/ml) regardless of life expectancy. Patients more suitable for watchful waiting are those who have an intermediate risk prostate cancer (T2b-T2c or Gleason 7 or PSA 10-20ng/ml) with <10 years life expectancy.

**Surgery – radical prostatectomy**

Radical prostatectomy involves the removal of the entire prostate gland including the seminal vesicles. It can be performed via an open, laparoscopic procedure or a robot-assisted laparoscopic approach. After removal of the gland, the surgeon reconstructs the bladder neck and re-anastamoses the urethra to the bladder. The aim of surgery is to provide a cure to men with localised prostate cancer. The selection of candidates for surgery would include localised prostate cancer, a life expectancy exceeding 10 years, and for patients to be medically fit. Prior to undergoing radical prostatectomy, patients are carefully counselled about the procedure itself, i.e. the approach (which could be open, laparoscopic or robotic-assisted laparoscopic), potential risks and complications, post-operative recovery and further treatment required if surgical margins were positive.

General complications that can occur with this surgery include bleeding, infection, thromboembolism or complications from general anaesthesia. Early specific complications that could arise from the surgery could include – damage to surrounding organs such as the obturator nerve, ureter or rectal injury; post-operative urinary catheter displacement; or urinary or lymphatic leak or lymphocoele. Late complications include – erectile dysfunction (which can affect >80% of men); urinary incontinence; or bladder neck stenosis.

Radical prostatectomy may be combined with pelvic lymphadenectomy dependent on the pre-operative suspicion of nodal metastatic disease. The precise indications and extent of pelvic lymphadenectomy when combined with radical prostatectomy are beyond the remit of this thesis.
Nerve-sparing radical prostatectomy involves removing the prostate gland and preserving the NVB to avoid complications such as erectile dysfunction. This technique does not compromise cancer control in appropriately selected patients. However, it is inappropriate in patients with advanced disease such as those with palpable extraprostatic tumour extension, extensive cancer in biopsy specimens, serum PSA>10ng/ml, biopsy Gleason score >7, poor quality erections pre-operatively or other medical conditions that may compromise erectile function (2).

In the early 1980s, Walsh observed in a male foetus cadaver that the nerves originating from the pelvic plexus that travelled along the prostate innervates the corpus cavernosum. He hypothesised that these nerves were likely to have been injured during radical prostatectomy and therefore resulted in erectile dysfunction (133). This plexus is situated between the rectum and urethra and penetrates the urogenital diaphragm near or in the muscular wall of the urethra. He also noted the NVB is a tubular structure that runs dorso-laterally to the prostate as an inferior extension to the pelvic plexus – synonymously known as the inferior hypogastric plexus (133, 134). Based on these findings, Walsh proposed an anatomical concept and modifications to the technique of radical prostatectomy where the lateral pelvic fascia is incised anterior to the NVB and the lateral pedicle is divided close to the prostate to avoid injury to the branches of the pelvic plexus that accompany capsular vessels of the prostate (134).

Further development has lead Costello et al. (135) in 2004 to publish more detailed findings about the NVB from human cadaver studies. Costello et al. demonstrated that most of the NVB descends distally and dorso-laterally to seminal vesicles (posterior nerves) and the anterior nerves course along the posterior-lateral border of the seminal vesicles. The anterior and posterior nerves of NVB are separated by a distance of 3cm at the base of the prostate. These nerves run distally towards the apex, converge at mid prostatic level, and then diverge again as they approach the prostate apex, where it is most variable in course and architecture (134).

Although nerve-sparing radical prostatectomy provides preservation of the NVBs and potentially a better quality of life for patients, it is still essential that the appropriate surgical candidates are chosen for this technique. It would not be unreasonable to assume that if there is macroscopic extracapsular extension, the nerve-sparing technique compromises cancer control (136). A predictor of extracapsular extension is related to PSA, Gleason score, tumour volume and perineural invasion in the biopsy specimen (137, 138). Shah et al. (139) published an article on an algorithm to guide surgeons on when to excise NVBs based on certain prognostic factors for extracapsular extension. The authors made the following recommendations:

- Ipsilateral NVBs were excised for Gleason 6 cancers with both perineural invasion and >50% of the biopsy specimen involved with cancers.
- Ipsilateral NVBs were excised for Gleason 7 cancers with perineural invasion or >30% of the biopsy specimen involved with the tumour.

- Ipsilateral NVBs were excised for Gleason 8 cancers with perineural invasion or >10% of the biopsy specimen involved with the tumour.

With the guide of the New York University algorithm, Shah et al. found that there was a decrease in positive surgical margins from 14% to 8%, whilst the proportion of NVBs spared increased from 85% to 92%.

As the NVBs are microscopic, meticulous haemostasis during a radical prostatectomy aids in identification of anatomical landmarks to allow preservation of the nerves. Control of the dorsal venous complex – which is important for haemostasis – involves ligating both proximal and distal structure before dividing it. Then, the prostatourethral junction is sharply incised. The tissue immediately lateral to the prostatovesical junction should not be disturbed as this is the location of the NVB as it courses through the membranous urethra (136). Lepor (136), in his review of surgical techniques for radical prostatectomy with nerve preservation, recommended six anastomotic sutures to be positioned into the urethra, with great care taken not to entrap the adjacent nerve located at the 3 and 9 o’clock positions. Following that, the posterior urethra is then divided. The anterior layer of Denonvillier’s fascia overlying the rectum is sharply incised and the prostate is bluntly mobilised off the rectum in the midline. There are two techniques for incising the visceral layer of the endopelvic fascia overlying the prostate and NVB as described by Lepor (136). The author has a preference of incising the fascia beginning at the apex when there is absence of significant biopsy artefact, dense adhesions or large apical tumour. If significant apical adhesions or large apical tumour is present, then the preference is to incise beginning at the bladder neck. When low volume, low grade disease is involved, the fascia is divided anteriorly on the prostate.

After the lateral pelvic fascia is incised, the prostate is retracted medially as the NVB is sharply and bluntly mobilised off the prostate. The Denonvillier’s fascia overlying the seminal vesicles and the vas deferens is incised and the rectum mobilised off these structures. The prostatic pedicle is divided beginning at the lateral margin of the seminal vesicle, staying close but not going through the prostate. The specimen is typically inspected to ensure that the prostate has not been accidentally incised.

Of note, the NVB is almost impossible to locate macroscopically, hence urologists rely on landmarks during radical prostatectomy for successful nerve preservation prostatectomy. However, a number of reasons can cause difficulty in locating the NVBs where the cavernous nerve is located. These include variation in location of the cavernous nerve, presence of overlying tissue, blood obscuring the operative field, or
poor exposure due to patient body habitus (140). As such, a hand-held nerve stimulator
device, the CaverMap™, was designed to help locate the cavernous nerve
intraoperatively. Further description of this device is beyond the scope of the thesis.

Robotic radical prostatectomy using the Da Vinci® robot was the next step to revolution
in the surgical treatment of prostate cancer. This technique allowed urologists to perform
certain aspects of a radical prostatectomy with greater surgical precision such as re-
anastamosis of urethra to bladder neck. Greater detail of technical aspect on how these
precise movements are created would be further explained in subsequent paragraphs.

The Da Vinci robot derived its name from Leonardo Da Vinci’s sketches and designs of
the humanoid robot. The famous Italian genius’ sketches of this mechanical man dating
back to 1495 were discovered when his notebook was uncovered in the 1950s. It
contained detailed sketches of a mechanical knight and almost certainly represented an
extension of the landmark anatomical research described in the Vitruvian Man (141). The
Industrial Revolution in the 18th century marked the influential phase in robotic
development as it lead to further development of key factors such as complex mechanics
and electricity. Another important early concept in robotic surgery was ‘telepresence’, a
term describing the sensation that one is in a location while being in another (141).
Telepresence robotic arms were developed in the 1950s and now form the basis of
robotic surgery. These master / slave manipulators were initially used in hazardous
environments such as the ocean floor, space or moving hazardous materials. Further
advancement of robotic surgery occurred in the 1980s with the development of
microelectronics, computing and charge-coupled devices needed for digital imaging,
video electronics and display technology. The USA agency DARPA (Defence Advanced
Research Project Agency) funding of a remote surgery program targeted towards
battlefield triage further launched the use of robotics in modern surgery in the early 1980s
(142).

The world’s first surgical robot was the ‘Arthrobot’, designed to assist in orthopaedic
procedures and used for the first time in Vancouver, Canada in 1983 (141). The first
application of robotic surgery in urology started in 1988 at Imperial College, London, UK
with the use of PROBOT in clinical trials to perform transurethral surgery (141, 143). The
PROBOT had the ability to replicate the same movements that a surgeon would perform
for a TURP.

In the 1990s two rivalling companies – Intuitive Surgical Inc and Computer Motion Inc –
fother developed robotic surgery from its initial military use to its application in civilian
surgeries. Computer Motion Inc developed the Zeus Surgical System the same time as
Intuitive Surgical Inc developed the Da Vinci robot. Both technologies depended on
laparoscopic patient-robot interface where trocars were placed into the abdomen and
insufflation of the peritoneal cavity was achieved with carbon dioxide. Eventually, Intuitive
Surgical Inc. acquired Computer Motion Inc. and became the sole provider of robotics surgery technology.

In 1998, the first da Vinci robotic surgery for robot-assisted mitral valve repair was performed in Leipzig, Germany (144). In 2000, the Food Drug and Administration (FDA) in the USA granted approval to the da Vinci robot for use in laparoscopic procedures. This was also the year that the first robot-assisted radical prostatectomy was performed in Paris, France (145).

The Da Vinci surgical system consists of a three multi-joint armed robot connected to a remote console. One arm controls the binocular endoscope and the other two control the endo-wrist instruments. Both 0° and 30° scopes are used at varying parts of the surgery to allow best visual fields. Two finger-controlled handles (the ‘masters’) found within the mobile console control the two robotic arms and camera. The operating surgeon is not required to scrub and is seated at the mobile console during the surgery. The view of two monitors is joined by a stereoscope which allows for 3D visualisation. Manipulation of the controls (masters) is transmitted to a computer that filters, scales and relays the surgeon’s movement to the robotic arms and instruments. The robotic joysticks can scale the hand movements 1:1, 3:1 or 5:1 movement at the tip of the instrument. This scaling allows for finer and better precision of certain steps in the operation. Studies have shown that, other than precision of movement, there is elimination of tremors and unintended movements. There is also no measurable delay between the movements of the handles in the console and the movement of the instruments within the patient. It was also found that the instruments allow 7° of liberty in their movement, more than the human hand (146).

Before the start of the case, the console is started and primed. The camera and lens are black and white balanced and calibrated to a cross bar. The viewing scope is adjusted to a comfortable height and viewing for the surgeon – allowing vision for both eyes to merge. The camera and robotic arm movements are tested and then the system is left on standby (146). The robot is draped by sterile plastic sheaths in preparation for surgery. The patient is placed in supine position with adequate padding and supports. The patient’s legs are placed in lithotomy position to allow the robotic system to be wheeled in and placed between the legs. Once the patient is prepped and draped, pneumoperitoneum can be achieved via the open Hasson technique through a 12mm umbilical port. Approximately 3.5-4 litres of gas volume with pressures set at 12-15mmHg are used to gain pneumoperitoneum. This is the port used for placement of the binocular scope. A total of six ports are placed for the surgery. Two 8mm ports are placed approximately 10cm from the midline on a line joining the anterior superior iliac spine to the umbilicus – these ports are used for the instrument arms. Instruments used include atraumatic graspers, needle drivers, scissors, suction, bipolar cautery and intracorporeal
clips. Two additional ports, 5mm ports, are placed in the iliac position for use by the first assistant. The assistant is limited to providing exposing the operative field, haemostasis, suction, irrigation and application of clips and electrocautery (145, 146). The prostate specimen is retrieved via the umbilical port at the end of the procedure.

**Radiotherapy**

Radiation therapy for localised prostate cancer is an alternative to surgery. However, currently, there are no prospective randomised controlled trials comparing radiotherapy to surgery. The various risks and benefits, treatment-related side effects and scheduling differences between surgery and radiation – as well as patient factors such as pre-existing co-morbidities – are often what drive treatment choice. Whilst surgical outcomes tend to improve with time due to late radiation side effects, radiation outcomes may actually deteriorate. For this reason, radiotherapy tends to be offered to patients who are older and those with greater co-morbidities.

There are multiple radiation delivery techniques, each with their own specific benefits and risks. Currently, options would include: external beam radiotherapy (EBRT) +/- 3D conformal therapy +/- intensity modulated radiotherapy (IMRT); low dose rate (LDR) brachytherapy; high dose rate (HDR) brachytherapy; and Cyberknife®.

**External beam radiotherapy**

External beam radiotherapy (EBRT) is one of the standard treatments for localised prostate cancer. It can be given to patients with prostate cancer in the following settings – primary EBRT, post-operative EBRT and palliative EBRT. Current technique involve giving ‘conformal’ radiotherapy focusing mainly on the prostate gland, minimising radiation being given to adjacent structures such as the rectum. Other techniques which include 3D conformal therapy and a further refinement, IMRT are discussed later.

The use of 3D CT planning has helped deliver EBRT in a more efficient manner. The treatment involves a 6-7 week course of daily treatments where up to 60-72Gy radiation is delivered. Some centres will use up to 80Gy to improve disease outcome (17).

Contraindications to EBRT include severe lower urinary tract symptoms (LUTS), inflammatory bowel disease and previous pelvic irradiation (17). Despite current contemporary techniques limiting exposure of radiation to other organs, patients are still counselled about the following side effects that can occur. They include transient LUTS, significant haematuria, moderate to severe gastrointestinal symptoms of bloody diarrhoea or pain, erectile dysfunction and potential risk of second solid pelvic malignancy (estimated 1 in 300) (17).

Outcome of EBRT is measured using PSA values. There have been numerous debates as to whether absolute levels, relative levels, rate of increase of PSA, or PSA density
should be used as outcome measures for radical EBRT. In 2005, the American Society for Therapeutic Radiology and Oncology (ASTRO) and the Radiation Therapy Oncology Group held a conference in Phoenix, USA to review the definition of biochemical failure in patients who underwent radical EBRT. The consensus was that a rise of 2ng/ml above the nadir PSA value is considered biochemical failure after EBRT with or without hormonal therapy (147).

In primary EBRT, patients with T1c-T2c N0 M0 prostate cancer can be offered this treatment as a primary treatment and an alternative to surgery. For patients with locally advanced, T3-T4 N0 M0 or high-risk prostate cancer – defined as Gleason ≥8 or PSA >20ng/ml or both (34) – EBRT is combined with ADT for a duration of 6 months to 3 years. A further refinement of 3D conformal radiotherapy – IMRT – is now becoming the gold standard in EBRT as it is able to provide higher doses to the prostate gland and seminal vesicles whilst reducing doses to surrounding structures therefore lowering toxicity (148).

Adjuvant EBRT after surgery is offered to patients with risk factors for recurrence such as positive surgical margins or high T stage disease. Adjuvant EBRT has been shown to reduce biochemical recurrence and improve cancer specific survival.

Salvage EBRT is offered to patients who have recurrence after radical prostatectomy. Cancer recurrence occurs from a range of 15-40 % of patients, with predominantly a pattern of local recurrence (149). Three important randomised controlled trials – European Organisation for Research and Treatment of Cancer [EORTC] 22911, Arbeitsgemeinschaft Radiologische Onkologie [ARO] 96-02 and Southwest Oncology Group [SWOG] 8796) (150-152) – comparing adjuvant EBRT versus observation after radical prostatectomy have shown a significant reduction in risk of local recurrence and PSA progression in patients, including the following adverse pathological features – extracapsular extension, seminal vesicle invasion or positive surgical margin (153). The amount of radiation dose delivered by these three trials was 60-64Gy.

The definition of biochemical failure after surgery is a greater than 0.2ng/ml with two consecutive increases after radical prostatectomy without evidence of systemic failure (154). This is the only therapy that would offer a potential cure. However, in order to achieve the best result, a low pre-radiation PSA level is necessary (155). The European Association of Urology (EAU) guidelines recommended that a PSA <0.5ng/ml is the recommended upper limit for salvage radiotherapy. The dose for salvage radiotherapy often administered is ≥68Gy (153).

Palliative EBRT is offered to patients with metastatic prostate cancer. The majority of these patients would have painful bony metastases which do not respond to systemic treatments or analgesia. Typically, single-fraction radiotherapy with a dose of 8Gy is
recommended for uncomplicated bony metastases (156). Patients can expect response from treatment from a few days up to a month, with complete pain relief reported in 20-50% of patients and partial relief of pain in 50-80% of patients (156). One of the emergencies in metastatic prostate cancer is spinal cord compression. If not treated promptly, it can lead to detrimental neurological effects such as paraplegia or quadriplegia. The gold standard treatment is steroids and surgical decompression followed by EBRT. If surgical decompression is not possible, then EBRT is combined with steroids (156).

Conformal radiotherapy treatment was first described by Prof. Takahashi in 1961 and was developed in the Department of Radiology, Nagoya University School of Medicine in Japan (157). Since the late 1980s, prostate cancer patients have been treated using this therapy at the University of Michigan, Memorial Sloan-Kettering Cancer Centre (MSKCC) and Fox Chase Cancer Centre (FCCC) (158). The development of conformal radiotherapy continued in 1994 when the National Cancer Institute (NCI) funded nine institutions to perform a dose escalation study in order to develop a national quality assurance centre for conformal radiotherapy (158).

Conformal therapy is a term that describes a strategy for matching the high-dose radiation region to the target volume whilst minimising radiation dose to surrounding healthy tissue. The target lesion and adjacent structures are contoured on CT image to produce a 3D reconstruction of the relevant organs – prostate, seminal vesicles, bladder and rectum. The treatment planning computer then determines the appropriate number and direction of treatment beams to give the desired dose distribution in the target. Each beam is viewed in the computer as a beams eye view of the target and the treatment aperture is shaped to conform to the shape of the target as seen by that individual treatment beam (158). A margin around the target is also added to allow for daily set-up variability.

IMRT is an advanced form of radiotherapy that uses high precision radiotherapy with computer-controlled linear accelerators to deliver precise amounts of radiation to the specified area of the tumour. It allows for a radiation dose to conform precisely to the 3D shape of the tumour by modulating or controlling the intensity of the radiation beam in multiple small doses. IMRT also allows for high doses of radiation to be delivered to accurate tumour locations while minimising the risk of radiation to surrounding healthy tissues.

Brachytherapy is another method of radiation therapy delivery which delivers a higher amount of radiation to the prostate gland in a highly conformal fashion. There are two distinct types of brachytherapy – LDR seed brachytherapy or HDR brachytherapy.
In LDR brachytherapy, patients would have approximately 75 to 125 radioactive seeds implanted permanently into the prostate gland via a perineal template under USS-guidance. Insertion of these seeds would involve the patient undergoing a light general or spinal anaesthesia; both isotopes Iodine-125 or Iridium-192 are commonly used, but, currently, only Iodine-125 is available in Australia (159). The planned radiotherapy dose is released over several months, depending on the isotope used.

LDR brachytherapy is reserved for patients with low-risk disease with the following characteristics – localised T1-2a, Gleason <6, PSA<10ng/ml, and life expectancy exceeding 5 years. Patients in the intermediate-risk or high-risk category are treated with a combination of HDR brachytherapy and EBRT. These are patients with T2b-2c, Gleason 7, PSA 10-20ng/ml. There are several relative contraindications for LDR brachytherapy — these include previous TURP (high risk of incontinence), large volume prostate (size >60ml) and moderate to severe LUTS (risk of retention) (17).

HDR brachytherapy is usually given in conjunction with EBRT in high risk cases. In HDR brachytherapy, a template is fixed to the perineum and transperineal catheters which are loaded with an isotope such as Iridium-192 are inserted into the prostate gland. The treatment planning uses CT or USS datasets. HDR brachytherapy dose is administered in two or large dose fractions typically over 24-48 hours. Patients are inpatients during the treatment and the perineal catheters are kept in place during this period. HDR brachytherapy can provide a maximal dose rate 1000-times higher than LDR brachytherapy. In the case of HDR brachytherapy, there are some special considerations which may be relative contraindications for patients which include the following (160):

- Prior rectal surgery.
- Prior pelvic radiation.
- Inflammatory bowel disease.
- Prior prostate radiation.
- Prior surgical urethral manipulation.
- Large prostate volume.
- Significant urinary symptoms.

The absolute contraindications for patients to have HDR brachytherapy as per the ABS (160) include the following: pre-existing rectal fistula; medically unsuitable for anaesthesia; and no proof that malignancy exists. Complications that can arise from brachytherapy include the following – LUTS, urinary retention, erectile dysfunction (up to 50%), urinary incontinence (5-20%), and perineal haematoma.
Cyberknife® is a novel form of radiation delivery for prostate cancer. The Cyberknife machine has a robotic arm that moves around the treatment couch to give radiation doses from different angles (161). Highly conformal doses can be achieved via tracking software to adjust for patient or tumour movement. Hypofractionated dose scheduling, i.e. increase dose per fraction reduces number of necessary sessions.

**Management of advanced prostate cancer**

**Hormone therapy**

Prostate cells are dependent on androgen for growth, function and proliferation. The testes are the main sources of androgen, i.e. testosterone (95% source). The adrenals synthesise the remaining 5% of androgens from cholesterol (17). Testosterone secretion is regulated by the hypothalamic-pituitary-gonadal axis (162). The anterior pituitary synthesises luteinising hormone (LH), stimulated by LH-releasing hormone (LHRH) produced by the hypothalamus. LH stimulates the Leydig cells of the testes to secrete testosterone. All prostate epithelial cells are dependent on androgens and would undergo programmed cell death without androgens. The same result is seen for prostate cancer cells which are also dependent on androgen. ADT has therefore been the main therapy of treatment for advanced prostate cancer.

The role of hormone manipulation in prostate cancer was first described by Huggins and Hodges in 1941 (163). They observed that castration or oestrogen treatment reduced the size of prostate gland and caused epithelial atrophy in both men and dogs. By applying the same treatment in prostate cancer, they found equally favourable responses and were awarded a Nobel Prize in recognition of this ground-breaking work.

The vast majority of prostate cancer patients respond to ADT. However, there are several predictors of a poor response to hormone therapy, including (17): ≥5 metastatic lesions at presentation; elevated alkaline phosphatase at presentation; anaemia at presentation; poor performance status at presentation; low serum testosterone at presentation; failure of bone pain to improve within 3 months of treatment; and failure of PSA to normalise within 6 months of treatment. The most common indication for initiating ADT is a rising PSA after failure of local therapy (164).

There are different types of ADT available (17): medical castration (LHRH agonists, LHRH antagonists, oestrogen); anti-androgens (steroidal and non-steroidal); surgical castration (bilateral orchidectomy); and maximal androgen blockade (medical or non-medical castration plus anti-androgen).

Patients are given a choice of either undergoing surgical or medical castration as both show equal efficacy. Patients diagnosed with advanced prostate cancer will have baseline PSA, full blood count, renal and liver function tests, imaging (renal USS or CT)
and a bone scan (17). The PSA levels are monitored on a 3-monthly basis, with periodic serum testosterone levels checked to ensure patients are within castrate level. Patients commenced on anti-androgen should have their liver function monitored every 3 months. Renal function should be rechecked if disease shows progression, and bone imaging repeated if clinically indicated. Patients are also given lifestyle advice on diet, exercise and treatment of erectile dysfunction prior to commencing ADT. Osteopenia / osteoporosis can occur secondary to androgen blockade and patients should be given calcium and vitamin D supplements. Biphosphonates which inhibit bone resorption have also been shown to benefit patients undergoing ADT for prostate cancer (165).

LHRH agonists were first developed in the 1980s. They provide an alternative to surgical ADT and are given as either subcutaneous or intramuscular injections either monthly, 3-, 6- or 12-monthly. The hypothalamus works on a feedback system where gonadotrophin releasing hormone (GnRH) and follicle-stimulating releasing hormone (FS-RH) will be released when testosterone levels run low. These two hormones then stimulate the pituitary gland to produce LH and follicle-stimulating hormone (FSH). LH and FSH will stimulate the Leydig cells in the testicle to produce testosterone. A total of 95% of testosterone is produced in the Leydig cells whilst the other 5% in the adrenal gland (166). LHRH agonist acts at the level of the pituitary gland by reducing the production of LH and FSH.

A phenomenon known as ‘tumour flare’ can occur in 20% patients initially started on LHRH agonist (17). When a patient is first commenced on LHRH agonist, the anterior pituitary is desensitised to the pulsatile release of natural LHRH by the analogue of LHRH, and FSH and LH will increase leading to transient serum testosterone levels surge – this phenomenon can lasts up to 2 weeks (166, 167). Catastrophic effects include spinal cord compression or fatal cardiovascular events due to hypercoagulation state. Other ‘flare’ effects include increased bone pain, acute bladder outlet obstruction or obstructive renal failure (154). To prevent ‘tumour flare’ from occurring, it is recommended that anti-androgens are started a week before and 2 weeks after the first dose of LHRH agonist. There are several types of LHRH agonists available including goserelin, histrelin, leuprolide, and triptorelin.

This group of ADT works by binding immediately and competitively to LHRH receptors in the pituitary gland. It results in a rapid decrease in LH, FSH and testosterone levels without any flare. The disadvantage of using LHRH antagonists is the lack of long-acting depot formulation. Several known medications under this class of ADT are Aberelix (given as an intramuscular injection every 2-4 weeks; also has potential anaphylaxis reaction) and Degarelix (two injections are required in the first month; given monthly as a maintenance dose).
Anti-androgens are administered as tablets. There are two types of anti-androgens – steroidal (including cyproterone acetate, megestrol acetate and medroxyprogesterone acetate) and non-steroidal (including nilutamide, flutamide and bicalutamide). They work by competing with androgens at receptor level. Non-steroidal anti-androgens give a slightly elevated or unchanged testosterone level whilst the steroidal class lowers testosterone level. Common side effects of anti-androgens include gynaecomastia, breast tenderness, occasional liver dysfunction, gastrointestinal upset, and decreased sexual libido and performance (17).

Bilateral orchidectomy was previously the standard treatment for prostate cancer ADT. A testosterone level of <50ng/dl was considered the castrate level in the past. With current modern techniques of testosterone, it is found that testosterone levels drop to 15ng/dl post-surgical castration and this had led a new definition of castrate level – testosterone level <20ng/dl (154). The surgery can be performed either under local or general anaesthesia. The testes are removed via a midline scrotal incision. The epididymis and testicular appendages are preserved to allow for some fullness in the scrotal sac and may psychologically benefit patients (17). One of the drawbacks of undergoing surgical castration is the irreversibility and, for some men, it is deemed a removal of their manhood.

Maximal androgen blockade involves using anti-androgen in combination with either medical or surgical castration (168). The theory of using MAB is based on the idea that after eliminating testicular androgens through surgical or medical castration, adrenal androgens still contribute to prostate cancer progression (2). Therefore, the aim is to ablate the source of androgen and inhibit LHRH with an aim to improve survival in advanced prostate cancer.

The three main controversies with regards to ADT and prostate cancer are (164) – timing of treatment (early versus deferred); a total androgen blockade; and intermittent versus continuous ADT.

The question with regards to timing of treatment started in the 1960s when diethylstilbestrol (DES) was used as ADT for prostate cancer. A landmark study by the Veterans Administration Cooperative Urological Research Group showed no difference in survival between patients who received DES and those who received a placebo (164, 169). A randomised controlled trial by the Medical Research Council Prostate Cancer Working Party Investigators on 900 patients with both locally advanced and metastatic cancer demonstrated a substantial survival benefit in the group that had immediate ADT. The authors found a 19% survival benefit in the non-metastatic group (170). Other studies – including a phase III trial by the Radiation Therapy Oncology Group – also found that patients with lymph node positive (by CT criteria) who had immediate ADT
with their radiotherapy had better survival rates – 50% versus 15% at 10 years (171). Therefore, early ADT is supported for better survival for patients.

There have been mixed results in several RCTs and meta-analysis with regards to the use MAB and improved survival in prostate cancer. Early experience in 1983 by Labrie et al (172) who used combination LHRH analogue and an anti-androgen in 30 patients found improved outcomes compared to standard treatment. More recently, the Prostate Cancer Trialists' Collaborative Group published a meta-analysis of 27 RCTs comparing MAB to standard ADT which demonstrated that overall, their meta-analysis had a 0 to 5% range of uncertainty about the true size of benefit gained from using MAB. The study also highlighted that studies which used cyproterone acetate, accounting for one fifth of the evidence had slightly unfavourable survival (5 year survival 15.4% MAB versus 18.1% AS alone). On the contrary, the use of nicalutamide and flutamide improved survival (5 year survival 27.6% MAB versus 24.7% AS alone).

The choice between intermittent versus continuous ADT remain controversial. Hussain et al. (173) found that there is no statistical difference in the survival benefit between the continuous ADT and the intermittent ADT group. In the intermittent group, there was reportedly better erectile function and mental health (p<0.001 and p=0.003 respectively) at month 3 but no reported benefit beyond that period (173). Niraula et al. (174) performed a meta-analysis comparing intermittent versus continuous ADT which showed no overall survival benefit proven for one method over the other. However, the authors recommend the use of intermittent ADT instead of continuous ADT for the treatment of men with relapsing, locally advanced or metastatic disease who achieve good initial response with ADT (174). This recommendation is based on evidence of cost, potential less toxicity and convenience.

Management of castration-resistant prostate cancer

The EAU guidelines have defined castration-resistant prostate cancer based on the following factors (154, 175, 176):

Castrate serum testosterone <50ng/dl or 1.7nmol/L

*Plus either:*

Biochemical progression: Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over nadir with PSA>2ng/ml.

*or*

Radiological progression: Two or more bone lesions on bone scan or enlargement of soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumours).

Further treatment is usually considered if the patient is still in castrate testosterone range. An additional anti-androgen such as bicalutamide for patients who have castration-
resistant therapy can benefit up to 20% patients. A PSA decline of approximately 50% has been demonstrated in these patients and a median survival time of 15 months (177).

The other possible treatment for patients with castrate-resistant prostate cancer is anti-androgen withdrawal. Approximately 20% of patients were found to have a median overall survival of 22 months after anti-androgen withdrawal treatment in a large multi-centre prospective trial (178). Oestrogens have also been used as second-line treatment of advanced prostate cancer. DES has previously been shown to improve the overall estimated survival of 63% at 2 years (179, 180); however, the drug, even at low doses, has been shown to cause deep vein thrombosis (30% of patients) and myocardial infarction (7% of patients).

The current standard first-line cytotoxic chemotherapy used is docetaxel. This agent acts by inducing apoptosis in cancer cells through TP-53 independent mechanisms (2). If patients fail docetaxal, abiraterone is PBS-listed for use post-chemotherapy and is on special access schemes pre-ADT.

Several other agents such as abiraterone acetate and enzalutamide have been trialled for castration-resistant prostate cancer patients who are chemonaive. A large randomised controlled trial comparing the use of abiraterone versus placebo, both combined with prednisolone, demonstrated promising results. There was significant radiological progression free survival and overall survival in patients receiving the treatment drug – median 16.5 versus 8.3 months (181). Another agent currently on trial, Enzalutamide (PREVAIL trial), also showed good results of significant improvement in time to radiological progression and overall survival (182).

**Palliative treatment for prostate cancer**

The involvement of a multi-disciplinary team of palliative care doctors and nurses and an acute pain team is important for patients with symptomatic metastatic prostate cancer. Patients may experience the following symptoms which can be debilitating – pain (particularly pain from bony metastases), spinal cord compression, LUTS or urinary retention, ureteric obstruction, and haematological disorders (anaemia, thrombocytopenia and coagulopathy).

Palliative radiotherapy can be given to treat painful bony metastases (183). Strontium-89 and samarium-153 isotope therapy can also palliate diffuse bony metastases but has adverse effects on platelets (184).

Spinal cord compression from spinal metastases in patients with prostate cancer is an oncological emergency. This is due to epidural compression from vertebral body metastases. Treatment available is high dose intravenous corticosteroids (e.g. dexamethasone). Spinal radiotherapy or occasionally neurosurgical spinal
decompression is also carried out. Surgery is the preferred option of treatment if pathological fracture, unknown tissue diagnosis or previous radiotherapy was given (17).

Patients with LUTS or urinary retention can be offered either surgery such as TURP or long-term catheterisation to alleviate symptoms. Bilateral ureteric obstruction can cause patients to be anuric or have signs of renal failure. This obstruction can be relieved either via bilateral percutaneous nephrostomy or ureteric stents. Retrograde ureteric stents placement can often be difficult as the prostatic malignancy may invade the trigone of the bladder and obscures the ureteric origins.

Haematological disorders – including anaemia, thrombocytopenia and coagulopathy from bone marrow replacement or ADT – can be treated with the necessary transfusions of blood products including packed red blood cells or platelets.